(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 104 764 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
**06.06.2001 Bulletin 2001/23**

(21) Application number: **99937053.9**

(22) Date of filing: **12.08.1999**

(51) Int Cl.[7]: **C07D 471/04**, C07D 471/14, C07D 491/113, C07D 495/14, A61K 31/435, A61K 31/47

(86) International application number:
**PCT/JP99/04381**

(87) International publication number:
**WO 00/09506 (24.02.2000 Gazette 2000/08)**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE**
Designated Extension States:
**AL LT LV MK RO SI**

(30) Priority: **12.08.1998 JP 24106298**
**30.07.1999 JP 21612599**

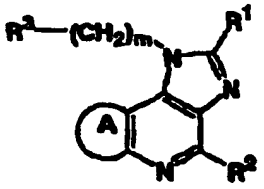
(71) Applicant: **HOKURIKU SEIYAKU CO., LTD.**
**Katsuyama-shi, Fukui 911-0813 (JP)**

(72) Inventors:
- **KATO, Hideo**
  **Katsuyama-shi, Fukui 911-0813 (JP)**
- **SAKAGUCHI, Jun**
  **Katsuyama-shi, Fukui 911-0813 (JP)**
- **AOYAMA, Makoto**
  **Katsuyama-shi, Fukui 911-0813 (JP)**
- **IZUMI, Tomoyuki**
  **Katsuyama-shi, Fukui 911-0813 (JP)**
- **KATO, Ken-ichi**
  **Katsuyama-shi, Fukui 911-0813 (JP)**

(74) Representative:
**Sternagel, Fleischer, Godemeyer & Partner**
**Patentanwälte**
**An den Gärten 7**
**51491 Overath (DE)**

# (54) 1H-IMIDAZOPYRIDINE DERIVATIVES

(57) 1H-Imidazopyridine derivatives represented by the following general formula or salts thereof:



wherein $R^1$ represents hydrogen atom, hydroxyl group, an alkyl group, a cycloalkyl group, styryl group, or an aryl group; $R^2$ represents hydrogen atom, an alkyl group, a halogen atom, hydroxyl group, amino group, a cyclic amino group, or phenoxy group; ring A represents a homocyclic or heterocyclic ring which may be substituted; $R^3$ represents a saturated nitrogen-containing heterocyclic group; and m represents an integer of from 0 to 3. The derivatives have excellent inhibitory actions against production of TNF or IL-1 and are extremely useful as preventive or therapeutic agents for diseases in which a cytokine is mediated.

EP 1 104 764 A1

Printed by Jouve, 75001 PARIS (FR)

## Description

### Technical Field

[0001] The present invention relates to novel 1H-imidazopyridine derivatives or salts thereof which have a potent inhibitory action against production of tumor necrotizing factor (TNF) or interleukin-1 (IL-1) and are useful as medicaments for preventive or therapeutic treatment of diseases of humans and animals, in which a cytokine such as TNF, IL-1 is mediated, which include chronic inflammatory diseases (e.g., rheumatic arthritis, osteoarthritis, etc.), allergic rhinitis, atopic dermatitis, contact dermatitis, asthma, sepsis, septic shock, various autoimmune diseases [autoimmune hemic diseases (e.g., hemolytic anemia, anaplastic anemia, idiopathic thrombocythemia, etc.), autoimmune intestinal diseases (e.g., ulcerative colitis, Crohn's disease, etc.), autoimmune corneitis (e.g., keratoconjunctivitis sicca, spring catarrh, etc.), endocrine ophthalmopathy, Graves disease, sarcoid granuloma, multiple sclerosis, systemic erythematodes, multiple chondritis, pachydermia, active chronic hepatitis, myasthenia gravis, psoriasis, interstitial pulmonary fibrosis and the like], diabetes, cancerous cachexia, HIV-infectious cachexia and the like.

### Background Art

[0002] Some compounds having 1H-imidazoquinoline structure are known which are analogous to the compounds of the present invention. Journal of Medicinal Chemistry, Vol. 11, p. 87 (1968) discloses 1-(2-piperidinoethyl)-1H-imidazo[4,5-c]-quinoline, Japanese Patent Unexamined Publication (KOKAI) No. Sho 60-123488/1985 discloses 1-isobutyl-1H-imidazo[4,5-c]quinoline-4-amine (general name: imiquimod) as a compound having an antiviral action, and Hungarian Patent Publication No. 34479 (Patent No. 190109) discloses 1-(2-diethylaminoethyl)-1H-imidazo[4,5-c]quinoline as a compound having analgesic and anticonvulsant actions. However, 1H-imidazopyridine derivatives as those according to the present invention have never been known so far.

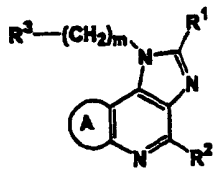
[0003] Moreover, the aforementioned imiquimod has been known to have an inducing action of a few kinds of cytokines such as interferon (IFN), TNF, IL-1 and the like, which is described in Journal of Interferon Research, Vol. 14, p. 81 (1994). However, 1H-imidazopyridine derivatives or 1H-imidazoquinoline derivatives having an inhibitory action against production of TNF or IL-1, which action is totally opposite to those taught by the aforementioned prior arts, have never been known so far.

### Disclosure of the Invention

[0004] An object of the present invention is to provide novel compounds which have excellent inhibitory actions against production of cytokines such as TNF and IL-1 and the like are useful as medicaments.

[0005] The inventors of the present invention made intensive studies to achieve the object. As a result, they found novel 1H-imidazopyridine derivatives which have an excellent inhibitory action against production of TNF or IL-1 and achieved the present invention.

[0006] The present invention thus relates to novel 1H-imidazopyridine derivatives represented by the following general formula (I) or salts thereof:

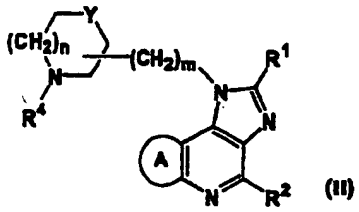


(I)

wherein $R^1$ represents hydrogen atom, hydroxyl group, an alkyl group which may have one or more substituents, a cycloalkyl group which may be substituted, a styryl group which may be substituted, or an aryl group which may have one or more substituents; $R^2$ represents hydrogen atom, an alkyl group, a halogen atom, hydroxyl group, an amino group which may have one or two substituents, a cyclic amino group which may be substituted, or a phenoxy group which may be substituted; ring A represents a homocyclic or heterocyclic ring which may be substituted with one or more alkyl groups, alkoxyl groups, or halogen atoms; $R^3$ represents a saturated nitrogen-containing heterocyclic group which may be substituted; and m represents an integer of from 0 to 3; provided that, when $R^3$ represents unsubstituted piperidino group, at least one of $R^1$ and $R^2$ is not hydrogen atom.

[0007] According to the second embodiment of the present invention, there are provided novel 1H-imidazopyridine

derivatives represented by the following general formula (II) or salts thereof:



(II)

wherein $R^1$, $R^2$, ring A and m have the same meanings as those defined above; $R^4$ represents hydrogen atom, an alkyl group, benzyl group, triphenylmethyl group, an alkanoyl group which may be substituted, an alkoxycarbonyl group, benzyloxycarbonyl group, a thiocarbamoyl group which may be substituted, an alkanesulfonyl group, a benzenesulfonyl group which may be substituted, or amidino group; Y represents methylene group, oxygen atom, sulfur atom, nitrogen atom, a group represented by NH, or a single bond; and n represents an integer of from 0 to 2.

**[0008]** According to the third embodiment of the present invention, there are provided, among the compounds represented by the aforementioned general formulas (I) and (II), the compounds wherein ring A is a benzene ring or a thiophene ring, or the salts thereof.

**[0009]** According to another aspect, there is provided a medicament which comprises as an active ingredient the compound represented by the aforementioned general formula (I) or (II), or a pharmacologically acceptable salt thereof. The medicament is useful for preventive or therapeutic treatment of diseases of mammals including humans, in which a cytokine such as TNF, IL-1 is mediated, which include chronic inflammatory diseases (e.g., rheumatic arthritis, osteoarthritis, etc.), allergic rhinitis, atopic dermatitis, contact dermatitis, asthma, sepsis, septic shock, various autoimmune diseases [autoimmune hemic diseases (e.g., hemolytic anemia, anaplastic anemia, idiopathic thrombocythemia, etc.), autoimmune intestinal diseases (e.g., ulcerative colitis, Crohn's disease, etc.), autoimmune corneitis (e.g., keratoconjunctivitis sicca, spring catarrh, etc.), endocrine ophthalmopathy, Graves disease, sarcoid granuloma, multiple sclerosis, systemic erythematodes, multiple chondritis, pachydermia, active chronic hepatitis, myasthenia gravis, psoriasis, interstitial pulmonary fibrosis and the like], diabetes, cancerous cachexia, HIV-infectious cachexia and the like.

**[0010]** According to a further aspect, there are provided a use of the compound represented by the aforementioned general formula (I) or (II), or a pharmacologically acceptable salt thereof for the manufacture of the aforementioned medicament; and a method for the preventive or therapeutic treatment of diseases in which a cytokine such as TNF, IL-1 is mediated, which comprises the step of administering a preventively or therapeutically effective amount of the compound represented by the aforementioned general formula (I) or (II), or a pharmacologically acceptable salt thereof to a mammal including a human. In addition, the present invention provides an inhibitor against production of tumor necrotizing factor (TNF) or interleukin-1 (IL-1) which comprises as an active ingredient the compound represented by the aforementioned general formula (I) or (II), or a pharmacologically acceptable salt thereof.

## Best Mode for Carrying Out the Invention

**[0011]** Specific explanations of the compounds of the aforementioned general formulas (I) and (II) of the present invention will be given below. The compounds represented by the aforementioned general formula (II) are characterized in that they have a specific saturated nitrogen-containing heterocyclic group which may have specific substituents as $R^3$ among the compounds represented by the aforementioned general formula (I). However, the scope of the present invention is not limited to the compounds represented by the aforementioned general formula (II), and it should be understood that any compounds having as $R^3$ a saturated nitrogen-containing heterocyclic group which may be substituted fall within the scope of the present invention.

**[0012]** In the aforementioned general formulas (I) and (II), examples of the alkyl group represented by $R^1$, $R^2$ or $R^4$ include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, n-hexyl group and the like.

**[0013]** Examples of the cycloalkyl group represented by $R^1$ include, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and the like. Examples of the aryl group represented by $R^1$ include, for example, phenyl group, 2-pyridyl group, 3-pyridyl group, 4-pyridyl group, 3-pyridazinyl group, 4-pyridazinyl group, 2-pyrimidinyl group, 4-pyrimidinyl group, 5-pyrimidinyl group, pyrazinyl group, 2-furyl group, 3-furyl group, 2-thienyl group, 3-thienyl group, 1-pyrrolyl group, 2-pyrrolyl group, 3-pyrrolyl group, 1-imidazolyl group, 2-imidazolyl group, 4-imidazolyl group, 1-pyrazolyl group, 3-pyrazolyl group, 4-pyrazolyl group, 5-pyrazolyl group, 2-oxazolyl group, 4-oxazolyl group, 3-isoxazolyl group, 4-isoxazolyl group, 5-isoxazolyl group, 2-thiazolyl group, 4-thiazolyl group, 5-thi-

azolyl group, 3-isothiazolyl group, 4-isothiazolyl group, 5-isothiazolyl group, 1,2,3-triazol-1-yl group, 1,2,3-triazol-4-yl group, 1,2,3-triazol-5-yl group, 1,2,4-triazol-1-yl group, 1,2,4-triazol-3-yl group, 1,2,4-triazol-5-yl group, 1-tetrazolyl group, 5-tetrazolyl group, 1,2,5-thiadiazol-3-yl group, 1-indolyl group, 2-indolyl group, 3-indolyl group and the like.

**[0014]** Examples of the halogen atom represented by $R^2$ include, for example, fluorine atom, chlorine atom, bromine atom, and iodine atom. Examples of the amino group which may have one or two substituents that is represented by $R^2$ include, for example, amino group, methylamino group, ethylamino group, n-propylamino group, isopropylamino group, cyclopropylamino group, cyclobutylamino group, cyclopentylamino group, cyclohexylamino group, dimethylamino group, diethylamino group, anilino group, pyridylamino group, 4-pyridylmethylamino group, benzylamino group, p-methoxybenzylamino group, dibenzylamino group and the like. Examples of the cyclic amino group represented by $R^2$ include, for example, 1-aziridinyl group, 1-azetidinyl group, 1-pyrrolidinyl group, piperidino group, 1-piperazinyl group, hexahydro-1H-azepin-1-yl group, hexahydro-1H-1,4-diazepin-1-yl group, morpholino group, 4-thiomorpholinyl group and the like.

**[0015]** Examples of the homocyclic or heterocyclic ring represented by ring A in the aforementioned general formulas (I) and (II) include, for example, benzene ring, cyclopentene ring, cyclohexene ring, cycloheptene ring, cyclooctene ring, cycloheptadiene ring, thiophene ring, furan ring, pyridine ring, pyrazine ring, pyrrole ring, thiazole ring, oxazole ring, azepine ring and the like. Examples of the alkyl group which may be substituted on the homocyclic or heterocyclic ring include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, n-hexyl group and the like. Examples of the alkoxyl group which may be substituted on the said ring include, for example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, n-pentyloxy group, isopentyloxy group, neopentyloxy group, n-hexyloxy group and the like. Examples of the halogen atom which may be substituted on the said ring include, for example, fluorine atom, chlorine atom, bromine atom, and iodine atom. The number and kind of these substituents are not particularly limited, and when two or more substituents exist, they may be the same or different.

**[0016]** In the aforementioned general formula (I), the saturated nitrogen-containing heterocyclic group represented by $R^3$ means a saturated nitrogen-containing heterocyclic group which has one or more nitrogen atoms as ring-constituting atom(s), and which may further have one or more oxygen atoms or sulfur atoms as ring-constituting atoms. Examples include 1-aziridinyl group, 2-aziridinyl group, 1-azetidinyl group, 2-azetidinyl group, 3-azetidinyl group, 1-pyrrolidinyl group, 2-pyrrolidinyl group, 3-pyrrolidinyl group, pyrazolidinyl group, imidazolidinyl group, piperidino group, 2-piperidyl group, 3-piperidyl group, 4-piperidyl group, 1-piperazinyl group, 2-piperazinyl group, hexahydro-1H-azepin-1-yl group, hexahydro-1H-azepin-2-yl group, hexahydro-1H-azepin-3-yl group, hexahydro-1H-azepin-4-yl group, hexahydro-1H-1,4-diazepin-1-yl group, hexahydro-1H-1,4-diazepin-2-yl group, hexahydro-1H-1,4-diazepin-5-yl group, hexahydro-1H-1,4-diazepin-6-yl group, 2-morpholinyl group, 3-morpholinyl group, morpholino group, 2-thiomorpholinyl group, 3-thiomorpholinyl group, 4-thiomorpholinyl group, 3-isoxazolidinyl group, 3-isothiazolidinyl group, 1,2,3-triazolidin-4-yl group, 1,2,4-triazolidin-3-yl group, 1,2,5-thiadiazolin-3-yl group and the like, and preferred groups include, for example, 3-piperidyl group, 4-piperidyl group, 1-piperazinyl group, 2-piperazinyl group, 3-pyrrolidinyl group, 2-azetidinyl group, 3-azetidinyl group, 2-morpholinyl group, 2-thiomorpholinyl group and the like.

**[0017]** In the aforementioned general formula (II), examples of the alkanoyl group which may be substituted that is represented by $R^4$ include, for example, formyl group, acetyl group, propionyl group, n-butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group, fluoroacetyl group, difluoroacetyl group, trifluoroacetyl group, chloroacetyl group, dichloroacetyl group, trichloroacetyl group and the like. Examples of the alkoxycarbonyl group represented by $R^4$ include, for example, methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, isobutoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, n-pentyloxycarbonyl group, n-hexyloxycarbonyl group and the like. Examples of the thiocarbamoyl group which may be substituted that is represented by $R^4$ include, for example, thiocarbamoyl group, methylthiocarbamoyl group, ethylthiocarbamoyl group, n-propylthiocarbamoyl group, isopropylthiocarbamoyl group, n-butylthiocarbamoyl group, isobutylthiocarbamoyl group, sec-butylthiocarbamoyl group, tert-butylthiocarbamoyl group and the like. Examples of the alkanesulfonyl group represented by $R^4$ include, for example, methanesulfonyl group, ethanesulfonyl group, n-propanesulfonyl group, n-butanesulfonyl group and the like.

**[0018]** In the present specification, with respect to the substituting/binding position of the terms "the aryl group", "the homocyclic or heterocyclic ring" and "saturated nitrogen-containing heterocyclic group", the terms herein used encompass any groups in their meanings which may substitute/bind at any position on a substitutable/bondable element among ring-constituting atoms, so long as the substituting/binding position is not particularly limited, as some examples are shown above.

**[0019]** In the aforementioned general formulas (I) and (II) of the present invention, when certain functional groups are referred to as "which may be substituted" or "which may have substitutents," the substituent may be any group so long as it can substitute on the functional groups. The number and kind of the substituent are not particularly limited, and when two or more substituents exist, they may be the same or different. Examples include halogen atoms such

as fluorine atom, chlorine atom, and bromine atom; hydroxyl group; alkyl groups such as methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, and n-hexyl group; trifluoromethyl group; aryl groups such as phenyl group, naphthyl group, and pyridyl group; alkoxyl groups such as methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, sec-butoxy group, and tert-butoxy group; aryloxy groups such as phenoxy group; amino groups which may be substituted such as amino group, methylamino group, ethylamino group, n-propylamino group, isopropylamino group, cyclopropylamino group, cyclobutylamino group, cyclopentylamino group, cyclohexylamino group, dimethylamino group, diethylamino group, anilino group, pyridylamino group, benzylamino group, dibenzylamino group, acetylamino group, trifluoroacetylamino group, tert-butoxycarbonylamino group, benzyloxycarbonylamino group, benzhydrylamino group, and triphenylmethylamino group; formyl group; alkanoyl groups such as acetyl group, propionyl group, n-butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group, fluoroacetyl group, difluoroacetyl group, trifluoroacetyl group, chloroacetyl group, dichloroacetyl group, and trichloroacetyl group; alkoxycarbonyl groups such as methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, isobutoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, n-pentyloxycarbonyl group, and n-hexyloxycarbonyl group; benzyloxycarbonyl group; carbamoyl group; alkylcarbamoyl groups such as methylcarbamoyl group, ethylcarbamoyl group, n-propylcarbamoyl group, isopropylcarbamoyl group, n-butylcarbamoyl group, isobutylcarbamoyl group, sec-butylcarbamoyl group, and tert-butylcarbamoyl group; thiocarbamoyl group; alkylthiocarbamoyl groups such as methylthiocarbamoyl group, ethylthiocarbamoyl group, n-propylthiocarbamoyl group, isopropylthiocarbamoyl group, n-butylthiocarbamoyl group, isobutylthiocarbamoyl group, sec-butylthiocarbamoyl group, and tert-butylthiocarbamoyl group; amidino group; alkylthio groups such as methylthio group; alkanesulfinyl groups such as methanesulfinyl group; alkanesulfonyl groups such as methanesulfonyl group, ethanesulfonyl group, n-propanesulfonyl group, and n-butanesulfonyl group; arylsulfonyl groups such as p-toluenesulfonyl group, p-methoxybenzenesulfonyl group, and p-fluorobenzenesulfonyl group; aralkyl groups such as benzyl group, naphthyl group, pyridylmethyl group, furfuryl group, and triphenylmethyl group; nitro group; cyano group; sulfamoyl group; oxo group; hydroxylmino group; alkoxylmino groups such as methoxylmino group, ethoxylmino group, n-propoxylmino group, and isopropoxylmino group; ethylenedioxy group and the like.

**[0020]** The compounds represented by the aforementioned general formulas (I) and (II) of the present invention can be converted into salts, preferably, pharmacologically acceptable salts, if desired; or free bases can be generated from the resulting salts.

**[0021]** Examples of the salts, preferably, the pharmacologically acceptable salts, of the compounds represented by the aforementioned general formulas (I) and (II) of the present invention include acid-addition salts, for example, salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, and phosphoric acid; and salts with organic acids such as acetic acid, propionic acid, butyric acid, formic acid, valeric acid, maleic acid, fumaric acid, citric acid, oxalic acid, malic acid, succinic acid, lactic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, mandelic acid, 10-camphorsulfonic acid, tartaric acid, stearic acid, gluconic acid, nicotinic acid, trifluoroacetic acid, and benzoic acid.

**[0022]** Among the compounds represented by the aforementioned general formulas (I) and (II) of the present invention, optical isomers may exist for compounds having asymmetric carbons. These optical active compounds and mixtures thereof fall within the scope of the present invention.

**[0023]** The compounds represented by the aforementioned general formulas (I) and (II) or the salts thereof according to the present invention can exist as any crystalline form depending on manufacturing conditions, or exist as any hydrate or solvate. These crystalline forms, hydrates or solvates, and mixtures thereof fall within the scope of the present invention.

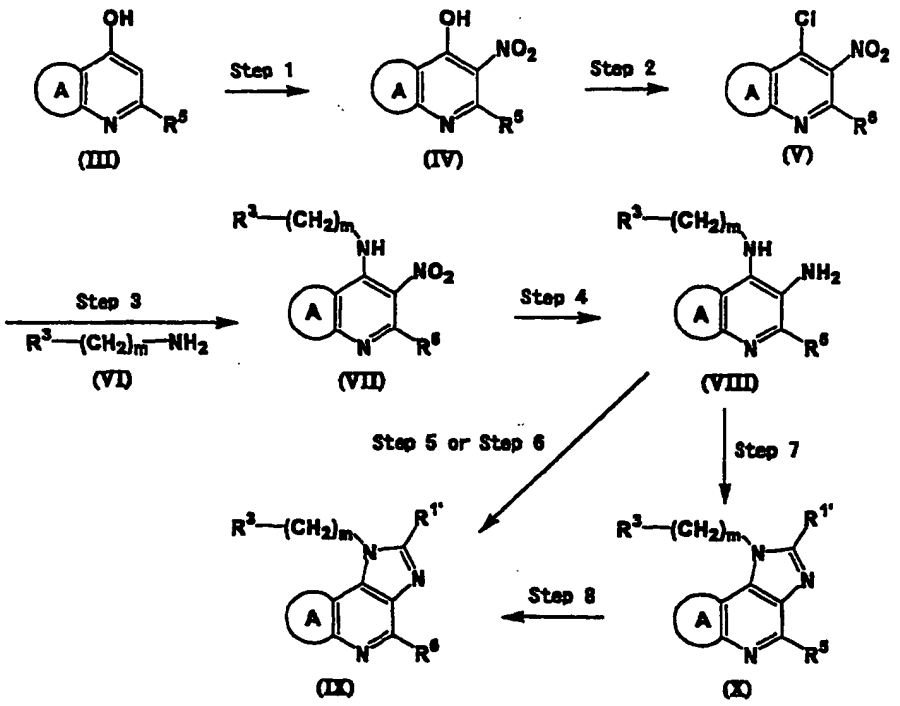
**[0024]** Preferred compounds of the present invention include, for example, the following compounds and salts thereof; however, the present invention is not limited to these examples:

(1) 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(2) 4,8-dichloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(3) 4-chloro-8-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(4) 4-chloro-8-methoxy-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(5) 4-chloro-2-phenyl-1-[2 -(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(6) 4,8-dichloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(7) 4-chloro-8-methyl-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5 -c]quinoline;
(8) 4-chloro-8-methoxy-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(9) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline;
(10) 4,8-dichloro-1-[2-(4-piperidyl)ethyl]-2 -trifluoromethyl-1H-imidazo[4,5-c]quinoline;
(11) 4-chloro-8-methyl-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline;
(12) 4-chloro-8-methoxy-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline;

(13) 4-chloro-2-(4-methylphenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(14) 4-chloro-2-(4-methoxyphenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(15) 4-chloro-2-(4-fluorophenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(16) 4-chloro-1-[2 -(4-piperidyl)ethyl]-2-(4-trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline;
(17) 4-chloro-2-(2-furyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(18) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-thienyl)-1H-imidazo[4,5-c]quinoline;
(19) 4-chloro-2-(2-imidazolyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(20) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-thiazolyl)-1H-imidazo[4,5-c]quinoline;
(21) 4-chloro-2-(5-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(22) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-pyrrolyl)-1H-imidazo[4,5-c]quinoline;
(23) 4-methyl-2-phenyl-1-[2 -(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(24) 2-(4-fluorophenyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(25) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(4-trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline;
(26) 2-(2-furyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(27) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-thienyl)-1H-imidazo[4,5-c]quinoline;
(28) 2-(2-imidazolyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(29) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-thiazolyl)-1H-imidazo[4,5-c]quinoline;
(30) 4-methyl-2-(3-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(31) 4-methyl-2-(5-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(32) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-pyrrolyl)-1H-imidazo[4,5-c]quinoline;
(33) 4-methyl-2-(1-methyl-2-pyrrolyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(34) 4-chloro-6,7,8,9-tetrahydro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(35) 4-chloro-6,7-dihydro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[5,4-d]cyclopenta[b]pyridine;
(36) 4-chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[5,4-d]thieno-[3,2-b]pyridine;
(37) 4-chloro-2-phenyl-1-[2-(3-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(38) 4-chloro-1-[2-(2-morpholinyl)ethyl]-2-phenyl-1H-imidazo[4,5-c]quinoline;
(39) 4-chloro-2-phenyl-1-[2-(1-piperazinyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(40) 4,6,7,8,9-pentachloro-2-ethoxymethyl-1-[2-(4-thiomorpholinyl)ethyl]-1H-imidazo[4,5-c]quinoline;
(41) 4-chloro-6,7,8,9-tetrahydro-2-hydroxymethyl-1-[2-(1-piperazinyl)ethyl]-1H-imidazo[5,4-d]cyclohepta[b]pyridine; and
(42) 4-chloro-2-(3-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline.

**[0025]** The novel 1H-imidazopyridine derivatives represented by the aforementioned general formula (I) or (II) according to the present invention can be prepared by various methods; however, the preparation methods of the compounds of the present invention are not limited thereto. In the following preparation methods, specific explanations for the compounds represented by the aforementioned general formula (I) will be given, and it is obvious that these preparation methods include the compounds represented by the aforementioned general formula (II).

**[0026]** As the first synthetic method of the compounds of the present invention, the following synthetic method can be used in accordance with the method disclosed in Japanese Patent Unexamined Publication (KOKAI) No. Hei 3-206078/1991 or Tetrahedron, Vol. 51, p. 5813 (1995):




wherein $R^5$ represents hydroxyl group or an alkyl group; $R^6$ represents chlorine atom or an alkyl group; $R^{1'}$ has the same meaning as that defined for $R^1$ (except for hydroxyl group); and $R^3$, m and ring A have the same meanings as those defined above.

**[0027]** In Step 1, the compound of the general formula (IV) can be obtained by allowing the compound represented by the general formula (III) to react with a nitrating agent such as concentrated nitric acid and fuming nitric acid in the presence or absence of acetic acid, sulfuric acid or the like at a temperature ranging from 0°C to 200°C.

**[0028]** In Step 2, the compound of the general formula (V) can be obtained by allowing the compound of the general formula (IV) to react with an appropriate chlorinating agent, for example, phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride, phosphorus pentachloride or the like, in the presence or absence of a solvent such as toluene at a temperature ranging from 0°C to 200°C.

**[0029]** In Step 3, the compound of the general formula (VII) can be obtained by reacting the amine represented by the general formula (VI) with the compound of the general formula (V) in a solvent such as N,N-dimethylformamide and toluene in the presence or absence of a base such as triethylamine and potassium carbonate at a temperature ranging from -10°C to the reflux temperature of a solvent.

**[0030]** In Step 4, the compound of the general formula (VIII) can be obtained by reducing the nitro group in the compound of the general formula (VII) according to an appropriate reducing method, for example, catalytic reduction using a metal catalyst such as platinum, Raney nickel, and palladium/carbon; reduction using nickel chloride and sodium borohydride; reduction using iron powder and hydrochloric acid and the like.

**[0031]** The reduction can be carried out in a solvent such as water, methanol, ethanol, and tetrahydrofuran, as well as a mixed solvent thereof, at a temperature ranging from 0°C to the reflux temperature of the solvent.

**[0032]** In Step 5, the compound of the general formula (IX) can be obtained by reacting the compound of the general formula (VIII) with a compound represented by the following general formula (XI), (XII) or (XIII):

$$R^{1'}C(OR)_3 \quad \text{(XI)}$$

$$R^{1'}COX \quad \text{(XII)}$$

$$(R^{1'}CO)_2O \qquad (XIII)$$

wherein R represents a lower alkyl group; X represents a halogen atom; $R^{1'}$ has the same meaning as that defined for $R^1$ (except for hydroxyl group),
in the presence or absence of a basic catalyst such as triethylamine, or an acid catalyst such as hydrochloric acid and p-toluenesulfonic acid, in the presence or absence of a solvent such as N,N-dimethylformamide, tetrahydrofuran, acetonitrile, xylene and toluene, at a temperature ranging from 0°C to 200°C.

**[0033]** In Step 6, as a method in place of Step 5, the compound of the general formula (IX) can be obtained by reacting the compound of the general formula (VIII) with a compound represented by the following general formula (XIV):

$$R^{1'}CHO \qquad (XIV)$$

wherein $R^{1'}$ has the same meaning as that defined for $R^1$ (except for hydroxyl group), in the presence of2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a solvent such as acetonitrile, 1,4-dioxane and tetrahydrofuran at a temperature ranging from 0°C to the reflux temperature of the solvent.

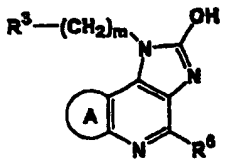
**[0034]** In Step 7, as a method in place of Step 5 or 6, the compound of the general formula (X) can be obtained by reacting the compound of the aforementioned general formula (VIII) with a compound represented by the following general formula (XV):

$$R^{1'}COOH \qquad (XV)$$

wherein $R^{1'}$ has the same meaning as that defined for $R^1$ (except for hydroxyl group), in the presence or absence of an acid catalyst such as hydrochloric acid and sulfuric acid, in the presence or absence of a solvent such as N,N-dimethylformamide and toluene, at a temperature ranging from 0°C to 200°C. Moreover, when $R^5$ represents hydroxyl group in the general formula (X), the compound of the general formula (IX) can be obtained by carrying out chlorination in Step 8.

**[0035]** The chlorination is carried out by protecting the compound of the general formula (X), if desired, at the nitrogen atom not bound to the $(CH_2)_m$ group, that is adjacent to the saturated nitrogen-containing heterocyclic group represented by $R^3$, with a protecting group such as alkanoyl groups in a conventional manner, then reacting with an appropriate chlorinating agent, for example, phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride, phosphorus pentachloride or the like in the presence or absence of a solvent such as toluene at a temperature ranging from 0°C to 200°C, and further deprotecting in a conventional manner, if desired, to obtain the compound of the general formula (IX) wherein $R^6$ is chlorine atom.

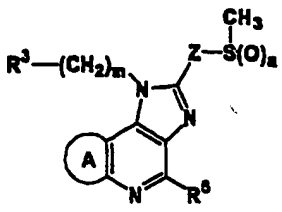
**[0036]** In the second synthetic method of the compounds of the present invention, the compound of the general formula (XVI):




(XVI)

wherein $R^3$, $R^6$, m and ring A have the same meanings as those defined above,
can be obtained by allowing the compound of the general formula (VIII) to react together with triphosgene in the presence of a base such as triethylamine and potassium carbonate in a solvent such as 1,2-dichloroethane, 1,4-dioxane, tetrahydrofuran, N,N-dimethylformamide and toluene at a temperature ranging from 0°C to the reflux temperature of a solvent.

**[0037]** In the third synthetic method of the compounds of the present invention, the compound of the general formula (XVII):



(XVII)

wherein Z represents an aromatic ring; the symbol "a" represents an integer of 1 or 2; and $R^3$, $R^6$, m and ring A have the same meanings as those defined above, can be obtained by carrying out suitable oxidation of the compound of the general formula (IX) which has an aryl group substituted with methylthio group as $R^{1'}$, after protecting, if desired, the nitrogen atom not bound to the $(CH_2)_m$ group, that is adjacent to the saturated nitrogen-containing heterocyclic group represented by $R^3$, with a protecting group such as alkanoyl groups in a conventional manner, and further deprotecting in a conventional manner, if desired.

**[0038]** The oxidation can be carried out in various manners according to the desired product. More specifically, the preparation can be made, when the symbol "a" represents an integer of 1, by reacting with an oxidizing agent, for example, chromic acid, hydrogen peroxide, m-chloroperbenzoic acid, sodium periodate, potassium periodate or the like, or when the symbol "a" represents an integer of 2, with an oxidizing agent, for example, chromic acid, hydrogen peroxide, m-chloroperbenzoic acid, osmium tetraoxide, ruthenium tetraoxide or the like, in a solvent such as tetrahydrofuran, 1,4-dioxane, 1,2-dichloroethane, methanol, acetone, and water, as well as a mixed solvent thereof, at a temperature ranging from 0°C to the reflux temperature of a solvent.

**[0039]** In the forth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^2$ is hydroxyl group can be obtained by allowing a compound of the general formula (I) wherein $R^2$ is chlorine atom to react with water and an appropriate acid or base in a solvent at a temperature ranging from 0°C to the reflux temperature of a solvent. Examples of the appropriate acid include, for example, organic acids such as formic acid, acetic acid, and trifluoroacetic acid, and mineral acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid. Examples of the appropriate base include, for example, hydroxides, carbonates and hydrogencarbonates of alkali metal such as sodium and potassium and of alkaline-earth metal such as magnesium and calcium and the like. Examples of the solvent include, for example, alcohols such as methanol, ethanol and n-propanol, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran and the like, and water-containing solvents thereof.

**[0040]** In the fifth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^2$ is fluorine atom, bromine atom or iodine atom and $R^1$ is $R^{1'}$ can be obtained by allowing a compound which is obtained by reacting the compound of the general formula (I) wherein $R^2$ is chlorine atom and $R^1$ is $R^{1'}$ or wherein $R^2$ is hydroxyl group and $R^1$ is $R^{1'}$ with trifluoromethanesulfonic anhydride, methanesulfonyl chloride or p-toluenesulfonyl chloride to react with a metal halide (e.g., potassium fluoride, sodium fluoride, lithium fluoride, potassium bromide, sodium bromide, potassium iodide, sodium iodide, etc.) in an aprotic solvent such as dimethylsulfoxide, N, N-dimethylformamide, and acetonitrile in the presence or absence of a phase-transfer catalyst such as tetraphenylphosphonium bromide, hexadecyltributylphosphonium bromide, and 18-crown-6 at a temperature ranging from 0°C to the reflux temperature of a solvent.

**[0041]** In the sixth synthetic method of the compounds of the present invention, the compound of the general formula (I), wherein $R^3$ is a saturated nitrogen-containing heterocyclic group of which the nitrogen atom that is not bound to the adjacent $(CH_2)_m$ group is deprotected, can be obtained by subjecting the compound of the general formula (I), wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having a protecting group such as alkanoyl groups, alkoxycarbonyl groups, benzyl group and trifluoromethyl group on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group, to deprotection with an acid or alkali, or to catalytic reduction with a metal catalyst, according to the type of the protecting group of the nitrogen atom.

**[0042]** The deprotection by using an acid or alkali can be carried out with an appropriate acid or base in the presence or absence of a cation scavenger such as anisole and thioanisole in a solvent. Examples of the solvent used include, for example, ethyl acetate, methylene chloride, 1,2-dichloroethane, 1,4-dioxane, methanol, ethanol, n-propanol, N,N-dimethylformamide, tetrahydrofuran, and water, as well as a mixed solvent thereof. Examples of the acid used include, for example, hydrochloric acid, an ethyl acetate solution of hydrogen chloride, an ethanolic solution of hydrogen chloride, sulfuric acid, hydrobromic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, formic acid, acetic acid and the like. Examples of the base include, for example, hydroxides, carbonates and hydrogencarbonates of alkali metal such as sodium and potassium, and of alkaline-earth metal such as magnesium and calcium and the like. The reaction can be carried out at a temperature ranging from 0°C to the reflux temperature of a solvent.

**[0043]** The catalytic reduction can be carried out by using an appropriate metal catalyst such as platinum, palladium/

carbon, Raney nickel, Pearlman's reagent in water, an alcohol such as methanol, ethanol and n-propanol, and acetic acid, as well as a mixed solvent thereof in the presence or absence of an acid such as hydrochloric acid at a temperature ranging from room temperature to the reflux temperature of the solvent under a pressure ranging from normal pressure to 200 kg/cm$^2$.

**[0044]** In the seventh synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^2$ is phenoxy group which may be substituted can be obtained by reacting the compound of the general formula (I) wherein $R^2$ is chlorine atom with a phenol derivative which may be substituted in the presence of a base such as sodium hydroxide and potassium hydroxide in the presence or absence of a solvent such as N,N-dimethylformamide and toluene at a temperature ranging from 0°C to 200°C.

**[0045]** In the eighth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^2$ is amino group can be obtained by subjecting the compound of the general formula (I) wherein $R^2$ is phenoxy group which may be substituted, that is obtained by the seventh synthetic method, to reaction together with ammonium acetate in the presence or absence of a solvent such as N,N-dimethylformamide and toluene at a temperature ranging from 0°C to 200°C.

**[0046]** In the ninth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^2$ is amino group which may have one or two substituents or a cyclic amino group which may be substituted can be obtained by subjecting the compound of the general formula (I) wherein $R^2$ is chlorine atom to reaction together with an amine derivative which may have one or two substituents or a cyclic amine derivative which may be substituted in the presence or absence of a base such as triethylamine, potassium carbonate and sodium hydride in the presence or absence of a solvent such as water, alcohols including methanol, ethanol and n-propanol, methylene chloride, 1,2-dichloroethane, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran and toluene at a temperature ranging from 0°C to 200°C under normal pressure or a pressurized condition.

**[0047]** In the tenth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^2$ is amino group can be obtained by subjecting the compound of the general formula (I) wherein $R^2$ is benzylamino group, dibenzylamino group, or p-methoxybenzylamino group, which is obtained in the ninth synthetic method, to catalytic reduction by using an appropriate metal catalyst, or by subjecting the compound of the general formula (I) wherein $R^2$ is p-methoxybenzylamino group to deprotection using an acid.

**[0048]** The catalytic reduction can be carried out with a metal catalyst such as palladium/carbon and Pearlman's reagent in a solvent such as alcohols including methanol and ethanol, and water, as well as a mixed solvent thereof at a temperature ranging from room temperature to the reflux temperature of a solvent in the presence or absence of an acid such as hydrochloric acid, acetic acid and formic acid, ammonium formate, cyclohexene, and cyclohexadiene under a pressure ranging from normal pressure to 200 kg/cm$^2$. The deprotection using an acid can be carried out with an acid such as hydrochloric acid, sulfuric acid, trifluoroacetic acid and trifluoromethanesulfonic acid in a solvent such as alcohols including methanol and ethanol, methylene chloride, 1,2-dichloroethane, 1,4-dioxane, tetrahydrofuran, toluene, and N,N-dimethylformamide in the presence or absence of a cation scavenger such as anisole and thioanisole at a temperature ranging from 0°C to the reflux temperature of a solvent.

**[0049]** In the eleventh synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group which is substituted with oxo group can be obtained by reacting the compound of the general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group which is substituted with ethylenedioxy group, with an acid such as hydrochloric acid, an ethyl acetate solution of hydrogen chloride, an ethanolic solution of hydrogen chloride, sulfuric acid, hydrobromic acid, trifluoroacetic acid, p-toluenesulfonic acid, formic acid and acetic acid in the presence or absence of a solvent such as ethyl acetate, methylene chloride, 1,4-dioxane, tetrahydrofuran, methanol, ethanol, n-propanol and N,N-dimethylformamide, or a water-containing solvent thereof at a temperature ranging from 0°C to 200°C.

**[0050]** In the twelfth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group which is substituted with hydroxyimino group or an alkoxyimino group can be obtained by reacting the compound of the general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group which is substituted with oxo group, that is obtained by the eleventh synthetic method, with a compound represented by the following general formula (XVIII):

$$R^7\text{-}O\text{-}NH_2 \qquad \text{(XVIII)}$$

wherein $R^7$ represents hydrogen atom or an alkyl group,

in the presence or absence of a base such as triethylamine, diisopropylethylamine, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and sodium acetate in a solvent such as alcohols including methanol, ethanol and n-propanol, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran, and toluene at a temperature ranging from 0°C

to the reflux temperature of a solvent.

**[0051]** In the thirteenth synthetic method of the compounds of the present invention, the compound of the general formula (I) wherein $R^2$ is hydrogen atom can be obtained by subjecting the compound of the general formula (I) wherein $R^2$ is chlorine atom to catalytic reduction using a metal catalyst such as platinum and palladium/carbon in the presence or absence of an acid such as hydrochloric acid and acetic acid in an alcohol solvent such as methanol and ethanol or a water-containing solvent thereof under normal pressure at a temperature ranging from room temperature to the reflux temperature of a solvent.

**[0052]** In the fourteenth synthetic method of the compounds of the present invention, the compound of the general formula (I), wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having an appropriate substituent on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group, can be obtained by reacting an appropriate reagent with the compound of the general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group not having a protecting group on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group.

**[0053]** The reaction can be carried out in the presence or absence of a solvent such as N,N-dimethylformamide, methylene chloride, tetrahydrofuran, toluene, pyridine, nitrobenzene, 1,2-dichloroethane, 1,4-dioxane, methanol, ethanol, n-propanol and water, as well as a mixed solvent thereof, in the presence or absence of a base such as triethylamine and potassium carbonate at a temperature ranging from 0°C to 200°C.

**[0054]** Examples of the appropriate reagent include, for example, alkyl halides, triphenylmethyl chloride, benzyl chloride, benzhydryl chloride, a mixture of formic acid and formalin, acetyl chloride, acetic anhydride, trifluoroacetic anhydride, benzoyl chloride, benzyl chlorocarbonate, ethyl chlorocarbonate, di-tert-butyl dicarbonate, sodium cyanate, alkyl isocyanates, sodium thiocyanate, alkyl isothiocyanates, 1H-pyrazole-1-carboxamidine, methanesulfonyl chloride, p-toluenesulfonyl chloride, p-fluorobenzenesulfonyl chloride, urethanes, alkylurethanes, thiourethanes, alkylthiourethanes and the like.

**[0055]** In the fifteenth synthetic method of the compounds of the present invention, the compound of the general formula (I), wherein $R^3$ is a saturated nitrogen-containing heterocyclic group substituted with an alkoxycarbonyl group or benzyloxycarbonyl group on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group, can be obtained by reacting the compound of the general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group substituted with an alkyl group or benzyl group on the nitrogen atom which is not bound to the adjacent $(CH_2)_m$ group with an alkyl chlorocarbonate or benzyl chlorocarbonate in the presence or absence of a solvent such as methylene chloride and toluene in the presence or absence of a base such as triethylamine and potassium carbonate at a temperature ranging from 0°C to 200°C.

**[0056]** Some of the compounds represented by the general formulas (III) to (VIII) which are starting materials or synthetic intermediates in the preparations of the compounds of the present invention are known compounds, which are disclosed in, for example, Journal of Medicinal Chemistry, Vol. 18, p. 726 (1975); Vol. 33, p. 1880 (1990); and Vol. 40, p. 1779 (1997); International Patent Publication No. 97/20820; European Patent Publication No. 223124 (1987) and the like, and can be prepared according to the method described therein. The preparations of some novel compounds will be described in reference examples.

**[0057]** The medicaments which comprise as an active ingredient the novel 1H-imidazopyridine derivative represented by the aforementioned general formula (I) or (II) or a salt thereof are generally administered as oral preparations in the forms of capsules, tablets, fine granules, granules, powders, syrups, dry syrups and the like, or as parenteral preparations in the forms of injections, suppositories, eye drops, eye ointments, ear drops, nasal drops, dermal preparations, inhalations and the like. These formulations can be manufactured according to conventional methods by addition of pharmacologically and pharmaceutically acceptable additives. For example, in the oral preparations and suppositories, pharmaceutical ingredients may be used such as excipients such as lactose, D-mannitol, corn starch, and crystalline cellulose; disintegrators such as carboxymethylcellulose and carboxymethylcellulose calcium; binders such as hydroxypropylcellulose, hydroxypropylmethylcellulose, and polyvinylpyrrolidone; lubricants such as magnesium stearate and talc; coating agents such as hydroxypropylmethylcellulose, sucrose, and titanium oxide; bases such as polyethylene glycol and hard fat and the like. In injections, or eye or ear drops and the like, pharmaceutical ingredients may be used such as solubilizers or solubilizing aids which may constitute aqueous preparations or those dissolved upon use such as distilled water for injection, physiological saline, and propylene glycol; pH modifiers such as inorganic or organic acids or bases; isotonicities such as sodium chloride, glucose, and glycerin; stabilizers and the like; and in eye ointments and dermal preparations, pharmaceutical ingredients which are suitable for ointments, creams and patches such as white vaseline, macrogols, glycerin, and cotton cloth.

**[0058]** A dose of the compounds of the present invention to a patient under therapeutic treatment is generally from about 0.1 to 1,000 mg in oral administration, and from about 0.01 to 500 mg in parenteral administration for an adult, which may depend on the symptoms of the patient. The aforementioned dose can be administered once a day or several times a day as divided portions. However, it is desirable that the aforementioned dose may suitably be increased or decreased according to a purpose of a therapeutic or preventive treatment, part or type of a disease, and the age or symptoms of a patient.

Examples

[0059] The present invention will be explained by referring to Reference Examples and Working Examples. However, the scope of the present invention is not limited to these examples.

[0060] The abbreviations in the tables have the following meanings: Ph, phenyl; Bn, benzyl; Boc, tert-butoxycarbonyl; Ac, acetyl; Ms, methanesulfonyl; Ts, p-toluenesulfonyl; Me, methyl; Et, ethyl; n-Bu, n-butyl.

Reference example 1

Ethyl N-triphenylmethyl-4-piperidinecarboxylate

[0061] To a solution of 76.5 g of ethyl isonipecotate and 81.5 ml of triethylamine in 750 ml of methylene chloride, 149 g of triphenylmethyl chloride divided in three portions was added portionwise at room temperature, and the mixture was stirred for 16 hours. The reaction mixture was added with water and extracted with methylene chloride. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting brown liquid was added with diisopropyl ether, and the precipitated crystals were collected by filtration and washed with diisopropyl ether to give 184 g of pale yellow crystals. Recrystallization from ethanol gave colorless prisms having the melting point of from 147.5 to 148.5°C.

| Elemental analysis for $C_{27}H_{29}NO_2$ | | | |
|---|---|---|---|
| Calculated % | C, 81.17; | H, 7.32; | N, 3.51 |
| Found % | C, 81.19; | H, 7.22; | N, 3.44 |

Reference example 2

N-Triphenylmethyl-4-piperidinemethanol

[0062] To a suspension of 10.6 g of lithium aluminium hydride in 300 ml of dried tetrahydrofuran, a solution of 112 g of ethyl N-triphenylmethyl-4-piperidine-carboxylate in 400 ml of dried tetrahydrofuran was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was added dropwise with a mixture of tetrahydrofuran and 10% aqueous sodium hydroxide solution under ice-cooling. An insoluble matter was filtered off and washed with tetrahydrofuran. The filtrates were combined and concentrated to give a colorless solid. The colorless solid was washed with methanol to give 84.2 g of colorless crystals. Recrystallization from methanol gave colorless crystals having the melting point of from 92 to 99.5°C.

| Elemental analysis for $C_{25}H_{27}NO$ | | | |
|---|---|---|---|
| Calculated % | C, 83.99; | H, 7.61; | N, 3.92 |
| Found % | C, 83.79; | H, 7.74; | N, 3.94 |

[0063] In accordance with the method of Reference example 2, the compound of Reference example 3 was obtained.

Reference example 3

N-Triphenylmethyl-4-piperidineethanol

[0064]

Appearance: colorless liquid
NMR spectrum δ ($CDCl_3$)ppm: 1.26(1H,brs), 1.36(2H,brs), 1.45-1.58(4H,m), 1.67(2H,d, J=12Hz), 3.05(2H,brs), 3.74(2H,t,J=6Hz), 7.14(3H,t,J=7.5Hz), 7.24(6H,t,J=7.5Hz), 7.46(6H,brs)
IR spectrum ν (liq.)$cm^{-1}$: 3416
Mass spectrum m/z: 371($M^+$)

Reference example 4

(N-Triphenylmethyl-4-piperidyl)methyl methanesulfonate

[0065] To a solution of 84.0 g of N-triphenylmethyl-4-piperidinemethanol and 36.2 ml of triethylamine in 420 ml of dried tetrahydrofuran, 18.3 ml of methanesulfonyl chloride was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 5.5 hours. The reaction mixture was added with water and extracted with diethyl ether. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting residue was added with a mixture of isopropanol and methanol, and the precipitated crystals were collected by filtration and washed with methanol to give 90.4 g of colorless crystals. Recrystallization from a mixture of methylene chloride and methanol gave colorless prisms having the melting point of from 129.5 to 134°C.

| Elemental analysis for $C_{26}H_{29}NO_3S$ | | | |
|---|---|---|---|
| Calculated % | C, 71.69; | H, 6.71; | N, 3.22 |
| Found % | C, 71.68; | H, 6.47; | N, 3.19 |

[0066] In accordance with the method of Reference example 4, the compound of Reference example 5 was obtained.

Reference example 5

2-(N-Triphenylmethyl-4-piperidyl)ethyl methanesulfonate

[0067]

Appearance: colorless crystals
Recrystallization solvent: methanol - diethyl ether
mp: 111.5-114°C

| Elemental analysis for $C_{27}H_{31}NO_3S$ | | | |
|---|---|---|---|
| Calculated % | C, 72.13; | H, 6.95; | N, 3.12 |
| Found % | C, 72.03; | H, 7.12; | N, 3.14 |

Reference example 6

4-Azidomethyl-N-triphenylmethylpiperidine

[0068] A suspension of 60.0 g of (N-triphenylmethyl-4-piperidyl)methyl methanesulfonate and 17.9 g of sodium azide in 300 ml of dried N,N-dimethyl-formamide was stirred at 70°C for 17 hours. After the reaction, an insoluble matter was filtered off and the filtrate was concentrated. The resulting residue was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting solid was washed successively with ethanol and n-hexane to give 42.6 g of colorless crystals. Recrystallization from a mixture of methanol and diethyl ether gave colorless crystals having the melting point of from 103.5 to 105.5°C.

| Elemental analysis for $C_{25}H_{26}N_4$ | | | |
|---|---|---|---|
| Calculated % | C, 78.50; | H, 6.85; | N, 14.65 |
| Found % | C, 78.45; | H, 6.74; | N, 14.82 |

Reference example 7

tert-Butyl 2-(2-azidoethyl)-1-piperidinecarboxylate

[0069] To a solution of 46.7 g of tert-butyl 2-(2-hydroxyethyl)-1-piperidine-carboxylate and 31.3 ml of triethylamine in 300 ml of dried tetrahydrofuran, 15.8 ml of methanesulfonyl chloride was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was added with water and extracted with

diethyl ether. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The resulting solid was washed with n-heptane to give 54.4 g of colorless crystals. And then, 22.9 g of sodium azide and 220 ml of N,N-dimethylformamide were added to the resulting crystals, and the mixture was stirred at 70°C for 4 hours. After the reaction, an insoluble matter was filtered off and the filtrate was concentrated. The resulting residue was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated to give 43.2 g of a yellow liquid.

NMR spectrum δ (DMSO-$d_6$)ppm: 1.20-1.32(1H,m),1.40(9H,s),1.48-1.58(5H,m),1.60-1 .68(1H,m),1.88-1.96(1H,m),2.71-2.78(1H,m),3.28(2H,t,J=6.5Hz),3.80-3.86(1H,m),4,19-4.25(1H,m)
IR spectrum ν (liq.)$cm^{-1}$: 2104,1692

Reference example 8

4-Oxo-1-piperidineacetonitrile

**[0070]** A suspension of 25.0 g of 4-piperidinone monohydrochloride monohydrate, 11.5 ml of chloroacetonitrile and 57.0 ml of diisopropylethylamine in 250 ml of tetrahydrofuran was refluxed for 10 hours. After the reaction, an insoluble matter was filtered off. The filtrate was added with saturated aqueous sodium hydrogencarbonate solution and extracted with a mixture of ethyl acetate and methanol (10:1). The extract was dried, and the solvent was evaporated to give brown crystals. The crystals were washed with a mixture of ethyl acetate and n-heptane to give 15.7 g of pale brown crystals.

NMR spectrum δ ($CDCl_3$)ppm: 2.53(4H,t,J=6Hz),2.91(4H,t,J=6Hz),3.66(2H,s)
IR spectrum ν (KBr)$cm^{-1}$: 2232,1714
Mass spectrum m/z: 138($M^+$)

**[0071]** In accordance with the method of Reference example 8, the compound of Reference example 9 was obtained.

Reference example 9

4-(tert-Butoxycarbonylamino)-1-piperidineacetonitrile

**[0072]**

Appearance: colorless needles
Recrystallization solvent: methanol
mp: 147-148°C

| Elemental analysis for $C_{12}H_{21}N_3O_2$ | | | |
|---|---|---|---|
| Calculated % | C, 60.23; | H, 8.84; | N, 17.56 |
| Found % | C, 60.08; | H, 8.63; | N, 17.55 |

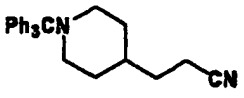
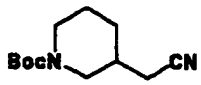
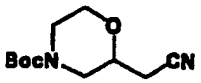
Reference example 10

N-Triphenylmethyl-4-piperidineacetonitrile

**[0073]** A suspension of 90.4 g of (N-triphenylmethyl-4-piperidyl)methyl methanesulfonate, 3.50 g of potassium iodide and 20.3 g of sodium cyanide in 400 ml of dried dimethylsulfoxide was stirred at 90°C for 5 hours. The reaction mixture was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and the solvent was evaporated to give a yellow liquid. The liquid was added with methanol, and the precipitated crystals were collected by filtration and washed with methanol to give 70.0 g of colorless crystals. Recrystallization from a mixture of methylene chloride and methanol gave colorless crystals having the melting point of from 138 to 139°C.

| Elemental analysis for $C_{26}H_{26}N_2$ | | | |
|---|---|---|---|
| Calculated % | C, 85.21; | H, 7.15; | N, 7.64 |
| Found % | C, 85.35; | H, 7.26; | N, 7.62 |

[0074] In accordance with the method of Reference example 10, the compounds of Reference examples 11 through 13 were obtained.

| Reference example | | Physical properties (Recrystallization solvent) |
|---|---|---|
| 11 |  | colorless crystals (MeOH-$Et_2O$)<br>mp.158.5-160.5°C<br>Elemental analysis for $C_{27}H_{22}N_2$<br>Calcd. %: C, 85.22; H, 7.42; N, 7.36<br>Found %: C, 85.21; H, 7.52; N, 7.34 |
| 12 |  | colorless prisms (iso-$Pr_2O$-n-Heptane)<br>mp.48-49°C<br>Elemental analysis for $C_{12}H_{20}N_2O_2$<br>Calcd. %: C, 64.26; H, 8.99; N, 12.49<br>Found %: C, 64.01; H, 9.24; N, 12.35 |
| 13 |  | colorless crystals (iso-$Pr_2O$)<br>mp.89-90°C<br>Elemental analysis for $C_{11}H_{18}N_2O_3$<br>Calcd. %: C, 58.39; H, 8.02; N, 12.38<br>Found %: C, 58.31; H, 8.01; N, 12.37 |

Reference example 14

N-Triphenylmethyl-4-piperidineacetic acid

[0075] A suspension of 21.2 g of N-triphenylmethyl-4-piperidineacetonitrile, 127 ml of 10% aqueous sodium hydroxide solution and 312 ml of ethanol was refluxed for 74 hours. The reaction mixture was neutralized with 10 % hydrochloric acid under ice-cooling, and then adjusted to pH 4-5 with 10% aqueous citric acid solution. The precipitated crystals were collected by filtration, and washed successively with water and methanol to give 23.6 g of colorless crystals. Recrystallization from a mixture of methanol and ethyl acetate gave colorless needles having the melting point of from 197 to 209°C (decomposition).

| Elemental analysis for $C_{28}H_{27}NO_2$ | | | |
|---|---|---|---|
| Calculated % | C, 81.01; | H, 7.06; | N, 3.63 |
| Found % | C, 80.85; | H, 7.17; | N, 3.70 |

Reference example 15

Ethyl N-triphenylmethyl-4-piperidineacetate

[0076] A suspension of 23.6 g of N-triphenylmethyl-4-piperidineacetic acid, 16.9 g of potassium carbonate and 5.0 ml of ethyl bromide in 230 ml of dried N,N-dimethylformamide was stirred at 90°C for 5 hours. After cooling, the reaction mixture was added with water and ethyl acetate, and the precipitated crystals were collected by filtration and washed with water to give 20.6 g of colorless crystals. Recrystallization from a mixture of methanol and tetrahydrofuran gave colorless crystals having the melting point of from 165 to 166°C.

| Elemental analysis for $C_{28}H_{31}NO_2$ | | | |
|---|---|---|---|
| Calculated % | C, 81.32; | H, 7.56; | N, 3.39 |
| Found % | C, 81.08; | H, 7.69; | N, 3.43 |

Reference example 16

4,4-Ethylenedioxy-1-piperidineacetonitrile

[0077] A solution of 10.0 g of 4-oxo-1-piperidineacetonitrile, 22.6 g of ethylene glycol and 0.62 g of anhydrous p-toluenesulfonic acid in 100 ml of toluene was refluxed for 6 hours with Dean-stark dehydrating apparatus. After cooling, the reaction mixture was added with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was dried, and the solvent was evaporated to give a pale brown liquid. The resulting liquid was purified by alumina column chromatography using ethyl acetate - n-heptane (1:3) as an eluting solvent to give 12.8 g of a colorless liquid.

NMR spectrum δ ($CDCl_3$)ppm : 1.78(4H,t,J=6Hz),2.69(4H,t,J=6Hz),3.52(2H,s),3.96(4 H,s)
IR spectrum ν (liq.)$cm^{-1}$: 2230,1094
Mass spectrum m/z: 182($M^+$)

Reference example 17

4-Aminomethyl-N-triphenylmethylpiperidine

[0078] To a suspension of 4.70 g of lithium aluminium hydride in 250 ml of dried tetrahydrofuran, a solution of 47.7 g of 4-azidomethyl-N-triphenylmethylpiperidine in 250 ml of dried tetrahydrofuran was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was added dropwise with a mixture of tetrahydrofuran and 10% aqueous sodium hydroxide solution under ice-cooling. An insoluble matter in the mixture was filtered off, and washed with tetrahydrofuran. The filtrate and the washings were combined and concentrated to give 48.1 g of a colorless liquid.

NMR spectrum δ ($CDCl_3$)ppm: 1.14(1H,brs),1.36(2H,brs),1.48(2H,qd,J=5,2.5Hz),1.68 (2H,d,J=11.5Hz),2.59(2H,d,J=6Hz),3.10(2H,brs),7.14(3H,t,J=7.5Hz),7.25(6H,t,J=7.5Hz ),7.47(6H,brs)
IR spectrum ν (liq.)$cm^{-1}$: 3056,3028
High resolution mass spectrum: Analysis for $C_{25}H_{28}N_2$

Calculated m/z: 356.2252
Found m/z: 356.2250

Reference example 18

4-(2-Aminoethyl)-N-triphenylmethylpiperidine

[0079] To a suspension of 21.7 g of lithium aluminium hydride in 300 ml of dried tetrahydrofuran, a solution of 28.1 g of concentrated sulfuric acid in 100 ml of dried tetrahydrofuran was added dropwise under ice-cooling, and the mixture was stirred for 30 minutes. And then, a solution of 70.0 g of N-triphenylmethyl-4-piperidineacetonitrile in 300 ml of dried tetrahydrofuran was added dropwise to the mixture under ice-cooling, and the mixture was stirred at room temperature for 6 hours. The reaction mixture was added dropwise with a mixture of tetrahydrofuran and 10% aqueous sodium

hydroxide solution under ice-cooling. An insoluble matter in the mixture was filtered off, and the filtrate was concentrated. The resulting residue was added with water and extracted with ethyl acetate. The extract was washed with saturated brine, and dried, and the solvent was evaporated to give 71.4 g of a colorless liquid.

NMR spectrum δ ($CDCl_3$)ppm: 1.18(1H,brs),1.35(2H,brs),1.40(2H,q,J=7.5Hz),1.48(2 H,qd,J=11.5,3Hz),1.63(2H, d,J=11.5Hz),2.67(2H,t,J=7.5Hz),3.05(2H,brs),7.14(3H,t,J=7. 5Hz),7.24(6H,t,J=7.5Hz),7.47(6H,brs)
IR spectrum ν (liq.)$cm^{-1}$: 3060,3032
High resolution mass spectrum: Analysis for $C_{26}H_{30}N_2$

Calculated m/z: 370.2409
Found m/z: 370.2400

[0080] In accordance with the method of Reference example 18, the compound of Reference example 19 was obtained.

Reference example 19

4-(3-Aminopropyl)-N-triphenylmethylpiperidine

[0081]

Appearance: colorless liquid
NMR spectrum δ (DMSO-$d_6$)ppm: 0.95-1.05(1H,m),1.19-1.35(6H,m),1.41( 2H,q,J=11.5Hz),1.62(2H,d,J=11.5Hz), 2.47(2H,t,J=6.5Hz),2.93(2H,d,J=11.5 Hz),7.15(3H,t,J=7.5Hz),7.28(6H,t,J=7.5Hz),7.38(6H,d,J=7.5Hz)
IR spectrum ν (liq.)$cm^{-1}$: 2972,2920

Reference example 20

tert-Butyl 2-(2-aminoethyl)-1-piperidinecarboxylate

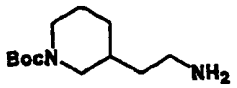
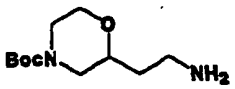
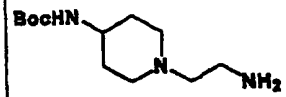
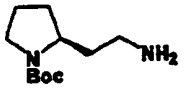
[0082] A suspension of 43.0 g of tert-butyl 2-(2-azidoethyl)-1-piperidinecarboxylate and 2.15 g of 5% palladium on carbon in 215 ml of methanol was catalytically hydrogenated at room temperature for 9 hours. After the reaction, the catalyst was filtered off, and the filtrate was concentrated to give 37.2 g of a colorless liquid. NMR spectrum δ (DMSO-$d_6$)ppm: 1.20-1.30(1H,m),1.38(9H,s),1.45-1.58(4H,m),1.72-1 .82(1H,m),2.34-2.47(2H,m),2.65-2.76(1H,m),3.18(2H,t, J=6Hz),3.78-3.85(1H,m),4.13-4. 20(1H,m)
IR spectrum ν (liq.)$cm^{-1}$: 2976,2936,1692

Reference example 21

1-(2-Aminoethyl)-4,4-ethylenedioxypiperidine

[0083] A suspension of 12.7 g of 4,4-ethylenedioxy-1-piperidineacetonitrile, 1.3 ml of Raney nickel and 113 ml of 2% methanolic solution of ammonia was catalytically hydrogenated at room temperature under 50 atm for 20 hours. After the reaction, the catalyst was filtered off, and the filtrate was concentrated. The resulting pale green liquid was purified by alumina column chromatography [eluting solvent: ethyl acetate →ethyl acetate - methanol (10:1)] to give 10.1 g of a colorless liquid.
NMR spectrum δ (DMSO-$d_6$)ppm : 1.58(4H,t,J=6Hz),2.37(2H,t,J=6.5Hz),2.42(4H,t,J= 6Hz),2.57(2H,t,J=6.5Hz),3.84 (4H,s)
IR spectrum ν (liq.)$cm^{-1}$: 2956,2884,1094

[0084] In accordance with the method of Reference example 21, the compounds of Reference examples 22 through 25 were obtained.

| Reference example | | Physical properties |
|---|---|---|
| 22 |  | colorless liquid<br>NMR spectrum δ (DMSO-$d_6$)ppm:1.02-1.12(1H,m),1.16-1.50(14H,m),1.53-1.60(1H,m),1.70-1.77(1H,m),2.56(2H,t,J=7.5Hz),2.75-2.83(1H,m),3.65-3.78(2H,m)<br>IR spectrum ν (liq.) $cm^{-1}$:2980,2936,1692 |
| 23 |  | bluish green liquid<br>NMR spectrum δ (DMSO-$d_6$)ppm:1.40(9H,s),1.55-2.00(2H,m),2.50-2.65(1H,m),2.75-2.90(1H,m),2.90-3.50(4H,m),3.60-3.90(3H,m)<br>IR spectrum ν (liq.) $cm^{-1}$:1700 |
| 24 |  | dark green liquid<br>NMR spectrum δ ($CDCl_3$)ppm:1.15(2H,brs),1.45(9H,s),1.85-2.00(2H,m),2.00-2.20(2H,m),2.30-2.50(2H,m),2.60-2.95(4H,m),3.40-3.60(2H,m),4.46(1H,brs)<br>IR spectrum ν (liq.) $cm^{-1}$:3332,1692 |
| 25 |  | colorless liquid<br>NMR spectrum δ (DMSO-$d_6$)ppm:1.39(9H,s),1.58-1.66(1H,m),1.68-1.90(5H,m),2.47(2H,t,J=7.5Hz),3.13-3.22(2H,m),3.68-3.76(1H,m)<br>IR spectrum ν (liq.) $cm^{-1}$:2972,2876,1696<br>Specific rotation<br>$[\alpha]_D^{20}$ : -54.3° (c=0.1, DMSO) |

Reference example 26

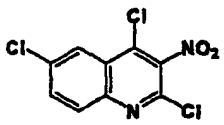
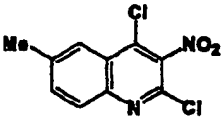
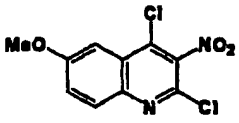
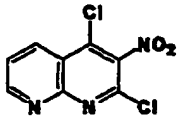
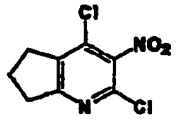
5,7-Dichloro-6-nitrothieno[3,2-b]pyridine

[0085] A mixture of 24.8 g of 4,5-dihydro-7-hydroxy-6-nitrothieno[3,2-b]pyridine-5-one and 87 ml of phosphorus oxychloride was stirred at 60°C for 24 hours. The reaction solution was concentrated and the residue was dissolved in a mixture of methylene chloride and methanol (10:1), and then the solution was poured into water. An insoluble matter was filtered off, and the organic solvent layer was separated. Furthermore, the aqueous layer was extracted with a mixture of methylene chloride and methanol (10:1). The combined organic solvent layer was dried, and the solvent was evaporated to give brown crystals. The resulting brown crystals were purified by silica gel column chromatography using ethyl acetate - n-hexane (1:3) as an eluting solvent to give 10.6 g of pale brown crystals. Recrystallization from n-hexane gave pale brown crystals having the melting point of from 96 to 97°C.

NMR spectrum δ ($CDCl_3$)ppm: 7.61(1H,d,J=5.5Hz),8.07(1H,d,J=5.5Hz)
IR spectrum ν (KBr)$cm^{-1}$: 1540,1368
Mass spectrum m/z : 248,250,252(M+,9:6:1)

[0086] In accordance with the method of Reference example 26, the compounds of Reference examples 27 through

32 were obtained.

| Reference example | | Physical properties (Recrystallization solvent) |
|---|---|---|
| 27 |  | pale brown crystals<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:7.87(1H,dd,J=9,2.5Hz),8.06(1H,d,J=9Hz),8.24(1H,d,J=2.5Hz) |
| 28 |  | brown crystals<br>NMR spectrum $\delta$ (DMSO-$d_6$)ppm:2.62(3H,s),7.78(1H,dd,J=9,2Hz),7.96(1H,d,J=2Hz),8.05(1H,d,J=9Hz) |
| 29 |  | pale brown crystals<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:4.01(3H,s),7.42(1H,d,J=2.5Hz),7.55(1H,dd,J=9,2.5Hz),7.99(1H,d,J=9Hz) |
| 30 |  | yellow crystals (Iso-PrOH)<br>mp,182-183°C<br>Elemental analysis for $C_9H_3Cl_2N_3O_2$<br>Calcd. %: C, 39.37; H, 1.24; N, 17.22<br>Found %: C, 39.37; H, 1.02; N, 17.25 |
| 31 |  | pale brown plates (n-Hexane)<br>mp,64-64.5°C<br>Elemental analysis for $C_9H_6Cl_2N_2O_2$<br>Calcd. %: C, 43.75; H, 3.26; N, 11.34<br>Found %: C, 43.77; H, 3.02; N, 11.44 |
| 32 |  | pale yellow plates (n-Hexane)<br>mp,94.5-95.5°C<br>Elemental analysis for $C_9H_6Cl_2N_2O_2$<br>Calcd. %: C, 41.23; H, 2.59; N, 12.02<br>Found %: C, 41.12; H, 2.64; N, 12.01 |

Reference example 33

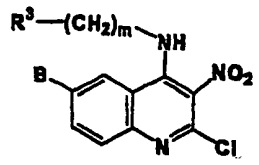
2-Chloro-3-nitro-4-[2-(N-triphenylmethyl-4-piperidyl)ethylamino]quinoline

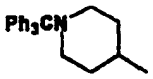
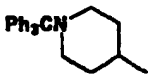
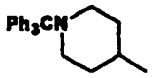
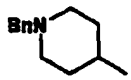
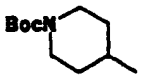
[0087] To a solution of 22.6 g of 2,4-dichloro-3-nitroquinoline and 13.0 ml of triethylamine in 60 ml of N,N-dimethylformamide, a solution of 23.0 g of 4-(2-aminoethyl)-N-triphenylmethylpiperidine in 40 ml of N,N-dimethylformamide was added dropwise with stirring under ice-cooling. The mixture was stirred at room temperature for 1 hour. The reaction mixture was added with ethyl acetate and water. The precipitated crystals were collected by filtration, and washed successively with ethyl acetate and diethyl ether to give 26.9 g of yellow crystals. Recrystallization from a mixture of N,N-dimethylformamide and ethyl acetate gave yellow crystals having the melting point of from 223.5 to 231°C (de-

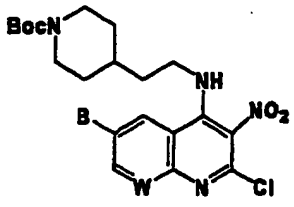
composition).

| Elemental analysis for $C_{35}H_{33}ClN_4O_2$ | | | |
|---|---|---|---|
| Calculated % | C, 72.84; | H, 5.76; | N, 9.71 |
| Found % | C, 72.64; | H, 5.80; | N, 9.82 |

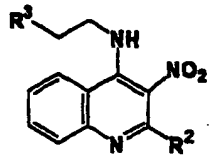
**[0088]** In accordance with the method of Reference example 33, the compounds of Reference examples 34 through 60 were obtained.

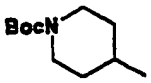
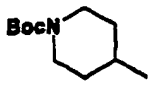
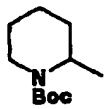
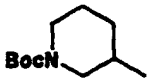
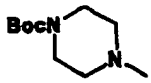


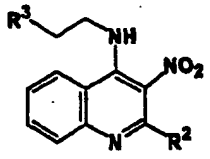
| Reference example | B | $R^2$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 34 | Cl |  | 2 | yellow crystals($CH_2Cl_2$–iso-$Pr_2O$)<br>mp,196.5–199.5℃(decomposition)<br>Elemental analysis for $C_{25}H_{22}Cl_2N_4O_2$<br>Calcd.%: C, 68.74; H, 5.27; N, 9.16<br>Found %:C, 68.47; H, 5.31; N, 9.18 |
| 35 | H |  | 1 | yellow crystals(MeOH–THF)<br>mp,214.5–225℃(decomposition)<br>Elemental analysis for $C_{24}H_{21}ClN_4O_2$<br>Calcd.%: C, 72.52; H, 5.55; N, 9.95<br>Found %:C, 72.54; H, 5.62; N, 9.82 |
| 36 | H |  | 3 | yellow crystals(MeOH–iso-$Pr_2O$)<br>mp,176.5–183℃(decomposition)<br>Elemental analysis for $C_{26}H_{25}ClN_4O_2$<br>Calcd.%: C, 73.14; H, 5.97; N, 9.48<br>Found %: C, 73.33; H, 6.04; N, 9.36 |
| 37 | H |  | 2 | yellow crystals(MeOH)<br>mp,128.5–129.5℃<br>Elemental analysis for $C_{23}H_{23}ClN_4O_2$<br>Calcd.%: C, 65.01; H, 5.93; N, 13.19<br>Found %: C, 64.96; H, 6.03; N, 13.27 |
| 38 | H |  | 0 | yellow crystals(AcOEt)<br>mp,199–202℃(decomposition)<br>Elemental analysis for $C_{19}H_{23}ClN_4O_4$<br>Calcd.%: C, 58.09; H, 5.70; N, 13.77<br>Found%: C, 58.04; H, 5.69; N, 13.77 |

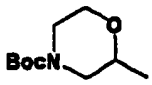
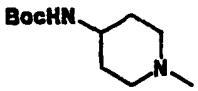
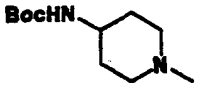
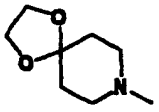


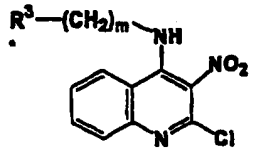
| Reference example | B | W | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 39 | Cl | CH | yellow crystals(MeOH)<br>mp.189.5–190.5℃<br>Elemental analysis for $C_{21}H_{28}Cl_2N_4O_4$<br>Calcd.%: C, 53.74; H, 5.58; N, 11.94<br>Found%: C, 53.61; H, 5.55; N, 11.67 |
| 40 | Me | CH | yellowish orange crystals (MeOH)<br>mp.185–186℃<br>Elemental analysis for $C_{22}H_{29}ClN_4O_4$<br>Calcd.%: C, 58.86; H, 6.51; N, 12.48<br>Found%: C, 58.72; H, 6.60; N, 12.39 |
| 41 | MeO | CH | yellowish orange crystals (MeOH)<br>mp.183.5–184.5℃<br>Elemental analysis for $C_{22}H_{29}ClN_4O_5$<br>Calcd.%: C, 56.83; H, 6.29; N, 12.05<br>Found%: C, 56.90; H, 6.34; N, 12.05 |
| 42 | H | N | yellow crystals(AcOEt–$Et_2O$)<br>mp.157.5–161℃<br>Elemental analysis for $C_{20}H_{29}ClN_5O_4$<br>Calcd.%: C, 55.11; H, 6.01; N, 16.07<br>Found%: C, 55.18; H, 6.10; N, 15.86 |

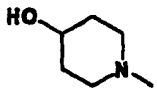
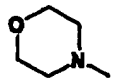
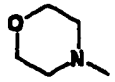
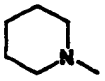


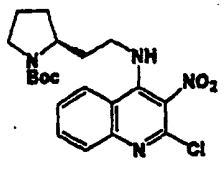
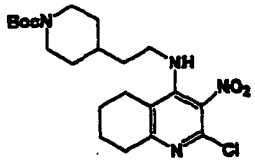
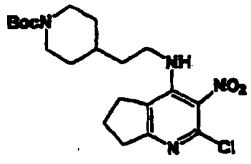
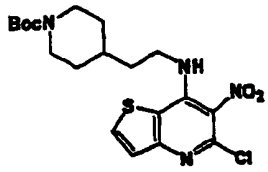
| Reference example | $R^2$ | $R^3$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 43 | Cl |  | yellow crystals(AcOEt-iso-$Pr_2O$)<br>mp,133-134℃<br>Elemental analysis for $C_{21}H_{27}ClN_4O_4$<br>Calcd.%: C, 57.99; H, 6.26; N, 12.88<br>Found%: C, 57.99; H, 6.34; N, 12.85 |
| 44 | Me |  | yellow crystals(EtOH)<br>mp,138-138.5℃<br>Elemental analysis for $C_{22}H_{30}N_4O_4$<br>Calcd.%: C, 63.75; H, 7.30; N, 13.52<br>Found%: C, 63.70; H, 7.49; N, 13.44 |
| 45 | Cl |  | yellow needles (AcOEt-n-Heptane)<br>mp,148.5-149℃<br>Elemental analysis for $C_{21}H_{27}ClN_4O_4$<br>Calcd.%: C, 57.99; H, 6.26; N, 12.88<br>Found%: C, 58.04; H, 6.27; N, 12.87 |
| 46 | Cl |  | yellow crystals(iso-$Pr_2O$)<br>mp,121-122.5℃<br>Elemental analysis for $C_{21}H_{27}ClN_4O_4$<br>Calcd.%: C, 57.99; H, 6.26; N, 12.88<br>Found%: C, 58.04; H, 6.32; N, 12.82 |
| 47 | Cl |  | yellow prisms (MeOH-iso-$Pr_2O$)<br>mp,155-157℃<br>Elemental analysis for $C_{23}H_{28}ClN_5O_4$<br>Calcd.%: C, 55.11; H, 6.01; N, 16.07<br>Found%: C, 54.92; H, 5.89; N, 16.00 |



| Reference example | $R^2$ | $R^3$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 48 | Cl |  | yellow crystals (MeOH)<br>mp,176.5–177.5℃<br>Elemental analysis for $C_{20}H_{25}ClN_4O_5$<br>Calcd.%: C, 54.98; H, 5.77; N, 12.82<br>Found%: C, 54.85; H, 5.76; N, 12.88 |
| 49 | Cl |  | yellow needles (AcOEt–iso-$Pr_2O$)<br>mp,150–150.5℃<br>Elemental analysis for $C_{21}H_{29}ClN_5O_4$<br>Calcd.%: C, 58.08; H, 6.27; N, 15.57<br>Found%: C, 55.92; H, 6.19; N, 15.59 |
| 50 | Me |  | yellow crystals (AcOEt)<br>mp,151–151.5℃<br>Elemental analysis for $C_{22}H_{31}N_5O_4$<br>Calcd.%: C, 61.52; H, 7.27; N, 16.31<br>Found%: C, 61.33; H, 7.14; N, 16.29 |
| 51 | Cl |  | yellow fine needles (AcOEt–iso-$Pr_2O$)<br>mp,119.5–123℃<br>Elemental analysis for $C_{18}H_{21}ClN_4O_4 \cdot 1/4H_2O$<br>Calcd.%: C, 54.41; H, 5.45; N, 14.10<br>Found%: C, 54.60; H, 5.45; N, 14.19 |



| Reference example | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 52 |  | 2 | yellow prisms (AcOEt-n-Heptane)<br>mp,121-123℃<br>Elemental analysis for $C_{16}H_{19}ClN_4O_3$<br>Calcd.%: C, 54.78; H, 5.46; N, 15.97<br>Found%: C, 54.70; H, 5.51; N, 15.93 |
| 53 |  | 2 | yellow crystals (MeOH)<br>mp,123-124℃<br>Elemental analysis for $C_{15}H_{17}ClN_4O_3$<br>Calcd.%: C, 53.50; H, 5.09; N, 16.64<br>Found%: C, 53.44; H, 4.94; N, 16.60 |
| 54 |  | 3 | yellowish brown crystals (MeOH)<br>mp,163-164℃<br>Elemental analysis for $C_{16}H_{19}ClN_4O_3$<br>Calcd.%: C, 54.78; H, 5.46; N, 15.97<br>Found%: C, 54.79; H, 5.38; N, 15.95 |
| 55 |  | 2 | yellowish brown crystals (MeOH)<br>mp,145-146℃<br>Elemental analysis for $C_{16}H_{19}ClN_4O_2$<br>Calcd.%: C, 57.40; H, 5.72; N, 16.73<br>Found%: C, 57.23; H, 5.75; N, 16.74 |
| 56 |  | 2 | yellow crystals (iso-$Pr_2O$)<br>mp,102.5-103℃<br>Elemental analysis for $C_{15}H_{17}ClN_4O_2$<br>Calcd.%: C, 56.16; H, 5.34; N, 17.47<br>Found%: C, 56.14; H, 5.37; N, 17.41 |

| Reference example | | Physical properties (Recrystallization solvent) |
|---|---|---|
| 57 |  | yellow prisms (iso-$Pr_2O$-n-Heptane)<br>mp.96–98°C<br>Elemental analysis for $C_{20}H_{25}ClN_4O_4$<br>Calcd.%: C, 57.07; H, 5.99; N, 13.31<br>Found%: C, 57.04; H, 5.92; N, 13.26<br>Specific rotation<br>$[\alpha]_D^{20}$: -97.3° (c=0.1, DMSO) |
| 58 |  | pale yellow crystals (MeOH)<br>mp.135–135.5°C<br>Elemental analysis for $C_{21}H_{31}ClN_4O_4$<br>Calcd.%: C, 57.46; H, 7.12; N, 12.76<br>Found%: C, 57.33; H, 7.15; N, 12.74 |
| 59 |  | red liquid<br>NMR spectrum $\delta$ (DMSO-$d_6$)ppm:0.98(2H,q,J=12.5Hz),1.20–1.30(1H,m),1.41(9H,s),1.59(2H,d,J=12.5Hz),2.04(2H,quin,J=8Hz),2.60–2.72(4H,m),2.79(2H,t,J=8Hz),2.93(2H,t,J=8Hz),3.21(2H,q,J=6.5Hz),3.89(2H,d,J=12.5Hz),6.52(1H,t,J=6.5Hz)<br>IR spectrum $\nu$ (liq.) $cm^{-1}$:1688,1526,1366 |
| 60 |  | orange crystals (iso-PrOH)<br>mp.148.5–150°C<br>Elemental analysis for $C_{19}H_{23}ClN_4O_4S$<br>Calcd.%: C, 51.75; H, 5.71; N, 12.71<br>Found%: C, 51.64; H, 5.80; N, 12.69 |

Reference example 61

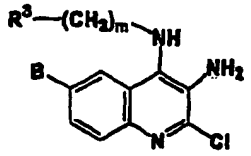
3-Amino-2-chloro-4-[2-(N-triphenylmethyl-4-piperidyl)ethylamino]quinoline

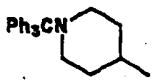
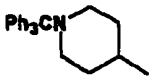
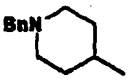
[0089] To a solution of 6.56g of nickel chloride hexahydrate and 22.3 ml of methanol in 100 ml of tetrahydrofuran, 2.09 g of sodium borohydride was added portionwise under ice-cooling, and then a suspension of 31.9 g of 2-chloro-3-nitro-4-[2-(N-triphenylmethyl-4-piperidyl)ethylamino]quinoline in 300 ml of tetrahydrofuran was added to the mixture. Successively, 8.35 g of sodium borohydride divided in four portions was added portionwise, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was added with 50 ml of water and an insoluble matter was filtered off, and then the extract was concentrated. The residue was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. The

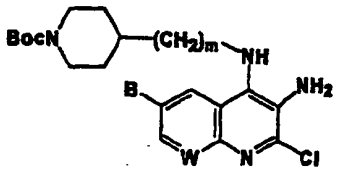
resulting pale green liquid was solidified with a mixture of ethyl acetate and diisopropyl ether, and the solid was washed successively with isopropanol and diisopropyl ether to give 20.1 g of pale green crystals. Recrystallization from isopropanol gave pale green crystals having the melting point of from 116 to 121°C.

| Elemental analysis for $C_{35}H_{35}ClN_4$ | | | |
|---|---|---|---|
| Calculated % | C, 76.83; | H, 6.45; | N, 10.24 |
| Found % | C, 76.74; | H, 6.54; | N, 10.17 |

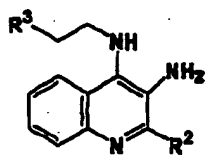
**[0090]** In accordance with the method of Reference example 61, the compounds of Reference examples 62 through 88 were obtained.

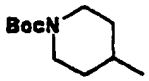
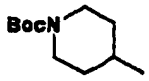
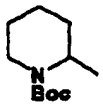
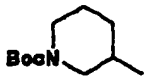
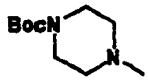


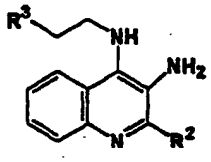
| Reference example | B | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 62 | Cl |  | 2 | colorless crystals (EtOH)<br>mp.197–198.5℃<br>Elemental analysis for $C_{25}H_{24}Cl_2N_4$<br>Calcd.%: C, 72.28; H, 5.89; N, 9.63<br>Found%: C, 72.45; H, 6.17; N, 9.34 |
| 63 | H |  | 1 | brown liquid<br>NMR spectrum δ (DMSO-$d_6$)ppm:1.20–1.45(3H,m),1.49(2H,q,J=11.5Hz),1.72(2H,d,J=11.5Hz),3.18(2H,t,J=7Hz),4.89(2H,s),5.09(1H,t,J=7Hz),7.14(3H,t,J=7.5Hz),7.27(6H,t,J=7.5Hz),7.35–7.45(8H,m),7.66(1H,d,J=8Hz),7.99(1H,d,J=8Hz)<br>IR spectrum ν (liq.) $cm^{-1}$:3356,3056 |
| 64 | H |  | 3 | colorless crystals (iso-$Pr_2O$)<br>mp.149–158℃<br>Elemental analysis for $C_{26}H_{27}ClN_4$<br>Calcd.%: C, 77.05; H, 6.65; N, 9.98<br>Found%: C, 76.93; H, 6.81; N, 9.97 |
| 65 | H |  | 2 | brown liquid<br>NMR spectrum δ ($CDCl_3$)ppm:1.20–1.50(3H,m),1.60(2H,q,J=7.5Hz),1.66(2H,d,J=11Hz),1.94(2H,t,J=11Hz),2.88(2H,d,J=11Hz),3.27(2H,q,J=7.5Hz),3.49(2H,s),3.79(1H,t,J=7.5Hz),4.06(2H,brs),7.20–7.35(5H,m),7.45(1H,td,J=8,1.5Hz),7.49(1H,td,J=8,1.5Hz),7.74(1H,dd,J=8,1.5Hz),7.89(1H,dd,J=8,1.5Hz)<br>IR spectrum ν (liq.) $cm^{-1}$:3360<br>Mass spectrum m/z:394,396($M^+$,3:1) |

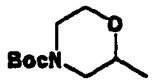
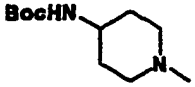
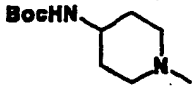


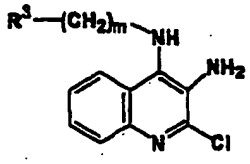
| Reference example | B | W | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 66 | H | CH | 0 | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,167-167.5℃<br>Elemental analysis for $C_{19}H_{25}ClN_4O_2$<br>Calcd.%: C, 60.55; H, 6.69; N, 14.87<br>Found%: C, 60.47; H, 6.83; N, 14.81 |
| 67 | Cl | CH | 2 | colorless crystals (iso-$Pr_2O$)<br>mp,154-155.5℃<br>Elemental analysis for $C_{21}H_{29}Cl_2N_4O_2$<br>Calcd.%: C, 57.40; H, 6.42; N, 12.75<br>Found%: C, 57.31; H, 6.37; N, 12.69 |
| 68 | Me | CH | 2 | colorless crystals (iso-$Pr_2O$)<br>mp,129-129.5℃<br>Elemental analysis for $C_{22}H_{31}ClN_4O_2$<br>Calcd.%: C, 63.07; H, 7.46; N, 13.37<br>Found%: C, 63.02; H, 7.56; N, 13.33 |
| 69 | MeO | CH | 2 | colorless crystals (iso-$Pr_2O$)<br>mp,140.5-141℃<br>Elemental analysis for $C_{22}H_{31}ClN_4O_3$<br>Calcd.%: C, 60.75; H, 7.18; N, 12.88<br>Found%: C, 60.61; H, 7.17; N, 12.81 |
| 70 | H | N | 2 | brown liquid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:1.14(2H,qd,J=12,3Hz),1.40-1.48(11H,m),1.50-1.70(5H,m),2.67(2H,t,J=12Hz),3.40(2H,t,J=7.5Hz),4.07(3H,brs),7.39(1H,dd,J=8.5,4.5Hz),8.29(1H,dd,J=8.5,2Hz),8.91(1H,dd,J=4.5,2Hz)<br>IR spectrum $\nu$ (liq.) $cm^{-1}$:3344,2928,1694<br>Mass spectrum m/z:405,407($M^+$,3:1) |

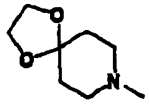
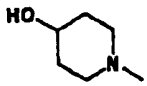
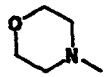
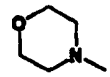


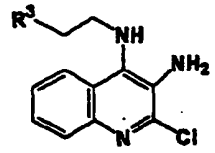
| Reference example | $R^2$ | $R^3$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 71 | Cl |  | colorless crystals (AcOEt–iso-$Pr_2O$)<br>mp.115.5–116℃<br>Elemental analysis for $C_{21}H_{29}ClN_4O_2$<br>Calcd.%: C, 62.29; H, 7.22; N, 13.84<br>Found%: C, 61.99; H, 7.28; N, 13.73 |
| 72 | Me |  | colorless crystals (iso-$Pr_2O$)<br>mp.132.5–134.5℃<br>Elemental analysis for $C_{22}H_{32}N_4O_2$<br>Calcd.%: C, 68.72; H, 8.39; N, 14.57<br>Found%: C, 68.65; H, 8.65; N, 14.48 |
| 73 | Cl |  | colorless prisms<br>(iso-$Pr_2O$–n-Heptane)<br>mp.108–110℃<br>Elemental analysis for $C_{21}H_{29}ClN_4O_2$<br>Calcd.%: C, 62.29; H, 7.22; N, 13.84<br>Found%: C, 62.18; H, 7.42; N, 13.81 |
| 74 | Cl |  | colorless crystals (iso-$Pr_2O$)<br>mp.104–106℃<br>Elemental analysis for $C_{21}H_{29}ClN_4O_2$<br>Calcd.%: C, 62.29; H, 7.22; N, 13.84<br>Found%: C, 62.11; H, 7.35; N, 13.79 |
| 75 | Cl |  | colorless prisms (AcOEt–iso-$Pr_2O$)<br>mp.128–128.5℃<br>Elemental analysis for $C_{20}H_{28}ClN_5O_2$<br>Calcd.%: C, 59.18; H, 6.95; N, 17.25<br>Found%: C, 59.16; H, 6.84; N, 17.15 |

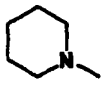
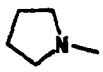


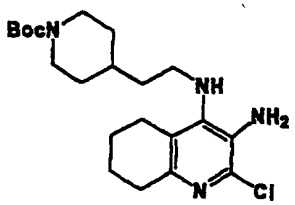
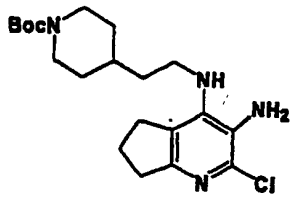
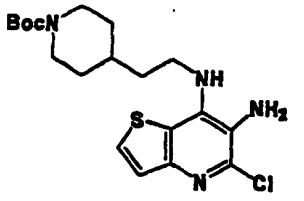
| Reference example | $R^2$ | $R^3$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 76 | Cl |  | green liquid<br>NMR spectrum δ ($CDCl_3$)ppm:1.47(9H,s),1.78(2H,q,J=6Hz),2.69(1H,brs),2.99(1H,brs),3.30-3.40(1H,m),3.50-3.55(1H,m),3.55-3.70(2H,m),3.75-4.05(3H,m),4.27(2H,brs),7.40-7.50(2H,m),7.80(1H,d,J=7.5Hz),7.90(1H,d,J=7.5Hz)<br>IR spectrum ν (liq.) $cm^{-1}$:3356,1696<br>Mass spectrum m/z:406,408($M^+$,3:1) |
| 77 | Cl |  | brown liquid<br>NMR spectrum δ ($CDCl_3$)ppm:1.40-1.55(2H,m),1.46(9H,s),2.00-2.05(2H,m),2.15-2.25(2H,m),2.45(2H,t,J=5.5Hz),2.80-2.90(2H,m),3.35(2H,t,J=5.5Hz),3.53(1H,brs),4.34(1H,brs),4.49(1H,brs),7.40-7.50(2H,m),7.85-7.90(2H,m)<br>IR spectrum ν (liq.) $cm^{-1}$:3356,1694<br>Mass spectrum m/z:419,421($M^+$,3:1) |
| 78 | Me |  | green liquid<br>NMR spectrum δ ($CDCl_3$)ppm:1.40-1.60(2H,m),1.46(9H,s),2.00-2.10(2H,m),2.10-2.25(2H,m),2.46(2H,t,J=5.5Hz),2.64(3H,s),2.85-2.90(2H,m),3.25(2H,t,J=5.5Hz),3.54(1H,brs),4.13(2H,brs),4.49(1H,brs),7.39(1H,t,J=8.5Hz),7.44(1H,t,J=8.5Hz),7.89(1H,d,J=8.5Hz),7.91(1H,d,J=8.5Hz)<br>IR spectrum ν (liq.) $cm^{-1}$:3352,1704<br>Mass spectrum m/z:399($M^+$) |



| Reference example | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 79 |  | 2 | colorless plates (AcOEt-iso-$Pr_2O$)<br>mp,104-105℃<br>Elemental analysis for $C_{20}H_{27}ClN_4O_2$<br>Calcd.%: C, 61.45; H, 6.96; N, 14.33<br>Found%: C, 61.49; H, 6.81; N, 14.35<br>Specific rotation<br>$[\alpha]_D^{29}$ : -20.9° (c=0.1, DMSO) |
| 80 |  | 2 | colorless crystals (iso-$Pr_2O$)<br>mp,96.5-99℃<br>Elemental analysis for $C_{15}H_{23}ClN_4O_2$<br>Calcd.%: C, 59.58; H, 6.39; N, 15.44<br>Found%: C, 59.30; H, 6.67; N, 15.30 |
| 81 |  | 2 | colorless crystals (AcOEt)<br>mp,126-128℃<br>Elemental analysis for $C_{16}H_{21}ClN_4O$<br>Calcd.%: C, 59.90; H, 6.60; N, 17.46<br>Found%: C, 59.71; H, 6.87; N, 17.32 |
| 82 |  | 2 | yellowish brown liquid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:2.49(2H,t,J=5Hz),2.50-2.60(4H,m),3.30-3.40(2H,m),3.75-3.85(4H,m),4.38(1H,brs),4.50(2H,brs),7.44(1H,td,J=8.5,1Hz),7.48(1H,td,J=8.5,1Hz),7.89(1H,dd,J=8.5,1Hz),7.91(1H,dd,J=8.5,1Hz)<br>IR spectrum $\nu$ (liq.) $cm^{-1}$:3348 |
| 83 |  | 3 | yellowish brown liquid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:1.89(2H,quin,J=6Hz),2.45-2.60(4H,m),2.63(2H,t,J=6Hz),3.30(2H,t,J=6Hz),3.78(4H,t,J=4.5Hz),4.50(3H,brs),7.44(1H,td,J=7.5,1Hz),7.47(1H,td,J=7.5,1Hz),7.83(1H,dd,J=7.5,1Hz),7.90(1H,dd,J=7.5,1Hz)<br>IR spectrum $\nu$ (liq.) $cm^{-1}$:3344<br>Mass spectrum m/z:320,322($M^+$, 3:1) |



| Reference example | $R^3$ | Physical properties |
|---|---|---|
| 84 |  | greenish brown liquid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:1.45-1.60(2H,m),1.60-1.70 (4H,m),2.35-2.60(4H,m),2.39(2H,t,J=5Hz),3.37(2H,t,J=5Hz),4.31(1H,brs),4.67(2H,brs),7.44(1H,td,J=7,1Hz),7.47(1H, td,J=7,1Hz),7.87(1H,dd,J=7,1Hz),7.94(1H,dd,J=7,1Hz)<br>IR spectrum $\nu$ (liq.) $cm^{-1}$:3432,3340<br>Mass spectrum m/z:304,306($M^+$,3:1) |
| 85 |  | dark brown liquid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:1.80-1.90(4H,m),2.57(2H,t, J=5.5Hz),2.60-2.70(4H,m),3.40(2H,t,J=5.5Hz),4.27(3H,brs ),7.43(1H,td,J=7.5,2Hz),7.46(1H,td,J=7.5,2Hz),7.87(1H,dd, J=7.5,2Hz),7.93(1H,dd,J=7.5,2Hz)<br>IR spectrum $\nu$ (liq.) $cm^{-1}$:3436,3348<br>Mass spectrum m/z:290,292($M^+$,3:1) |

| Reference example | | Physical properties (Recrystallization solvent) |
|---|---|---|
| 86 |  | colorless crystals (iso-$Pr_2O$)<br>mp.130.5–131.5°C<br>Elemental analysis for $C_{21}H_{23}ClN_4O_2$<br>Calcd.%: C, 61.67; H, 8.13; N, 13.70<br>Found%: C, 61.52; H, 8.29; N, 13.65 |
| 87 |  | colorless crystals<br>($ClCH_2CH_2Cl$-iso-$Pr_2O$)<br>mp.141.5–142.5°C<br>Elemental analysis for $C_{20}H_{21}ClN_4O_2$<br>Calcd.%: C, 60.82; H, 7.91; N, 14.19<br>Found%: C, 60.63; H, 7.80; N, 14.03 |
| 88 |  | gray crystals (AcOEt)<br>mp.168–169°C<br>Elemental analysis for $C_{18}H_{27}ClN_4O_2S$<br>Calcd.%: C, 55.53; H, 6.62; N, 13.63<br>Found%: C, 55.54; H, 6.87; N, 13.63 |

Example 1

4-Chloro-1-[2-(N-triphenylmethyl-4-piperidyl)ethyl]-1H-imidazo[4,5-c]-quinoline

**[0091]** A solution of 19.9 g of 3-amino-2-chloro-4-[2-(N-triphenylmethyl-4-piperidyl)-ethylamino]quinoline, 24.1 ml of ethyl orthoformate and 0.68 g of p-toluenesulfonic acid monohydrate in 200 ml of toluene was refluxed for 6 hours. After cooling, the precipitated crystals were collected by filtration, and washed with diisopropyl ether to give 16.4 g of colorless crystals. Recrystallization from a mixture of methanol and tetrahydrofuran gave colorless crystals having the melting point of from 229 to 234.5°C (decomposition).

| Elemental analysis for $C_{38}H_{33}ClN_4$ | | | |
|---|---|---|---|
| Calculated % | C, 77.61; | H, 5.97; | N, 10.06 |
| Found % | C, 77.50; | H, 5.98; | N, 9.95 |

Example 2

4-Chloro-2-trifluoromethyl-1-[2-(N-triphenylmethyl-4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

**[0092]** To a solution of 2.50 g of 3-amino-2-chloro-4-[2-(N-triphenylmethyl-4-piperidyl)ethylamino]quinoline and 0.76 ml of triethylamine in 60 ml of dried tetrahydrofuran, a solution of 0.63 ml of trifluoroacetic anhydride in 40 ml of dried tetrahydrofuran was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent of the reaction mixture was evaporated, and the residue was added with water and saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated. A solution of 3.03 g of the resulting pale yellow solid and 0.30 g of p-toluenesulfonic acid monohydrate in 100 ml of toluene was refluxed for 20 hours. After the reaction,

the solvent was evaporated, and the residue was added with methanol and acetone. The precipitated crystals were collected by filtration to give 1.79 g of colorless crystals.
NMR spectrum δ (DMSO-$d_6$)ppm : 1.35-1.55(3H,m),1.59(2H,q,J=11Hz),1.77(2H,d,J=11Hz),1.80-1.90(2H,m),2.98(2H, brs),4.75(2H,t,J=8.5Hz),7.17(3H,t,J=8Hz),7.30(6H,t,J=8Hz),7.41(6H,brs),7.84(1H,td,J=7.5,2Hz),7.87(1H,td, J=7.5,2Hz),8.16(1H,dd,J=7.5,2Hz ),8.34(1H,dd,J=7.5,2Hz)

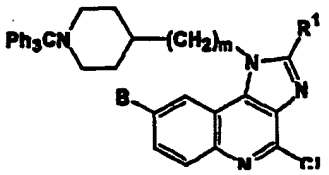
Example 3

tert-Butyl 4-[2-(4-methyl-2 -phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate

[0093] A solution of 0.65 g of tert-butyl 4-[2-[(3-amino-2-methylquinolin-4-yl)amino]-ethyl]-1-piperidinecarboxylate, 0.29 g of benzaldehyde and 0.08 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 5 ml of tetrahydrofuran was stirred at room temperature for 3 days. The reaction mixture was added with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried, and the solvent was evaporated to give a reddish brown liquid. The resulting liquid was purified by silica gel column chromatography using ethyl acetate - n-heptane (1:1) as an eluting solvent, and washed with diisopropyl ether to give 0.55 g of a colorless solid. Recrystallization from diisopropyl ether gave colorless crystals having the melting point of from 146 to 146.5°C.

| Elemental analysis for $C_{29}H_{34}N_4O_2$ | | | |
|---|---|---|---|
| Calculated % | C, 74.01; | H, 7.28; | N, 11.91 |
| Found % | C, 73.95; | H, 7.54; | N, 11.84 |

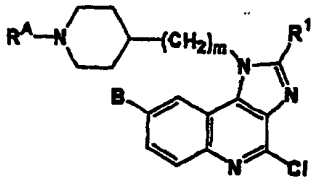
[0094] In accordance with the methods of Examples 1 through 3, the compounds of Examples 4 through 72 were obtained.



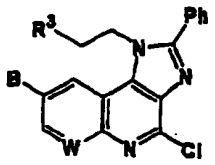

| Example | $R^1$ | B | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 4 | H | H | 1 | colorless crystals (MeOH)<br>mp,232-239°C (decomposition)<br>Elemental analysis for $C_{35}H_{31}ClN_4$<br>Calcd.%: C, 77.40; H, 5.75; N, 10.32<br>Found%: C, 77.35; H, 5.79; N, 10.19 |
| 5 | Ph | H | 1 | pale yellow crystals (AcOEt)<br>mp,165-168°C (decomposition)<br>Elemental analysis for $C_{41}H_{35}ClN_4$<br>Calcd.%: C, 79.53; H, 5.70; N, 9.05<br>Found%: G, 79.29; H, 5.74; N, 9.05 |
| 6 | H | Cl | 2 | colorless crystals (MeOH)<br>mp,268-268°C (decomposition)<br>Elemental analysis for $C_{38}H_{32}Cl_2N_4$<br>Calcd.%: C, 73.09; H, 5.45; N, 9.47<br>Found%: C, 73.15; H, 5.54; N, 9.41 |

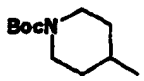
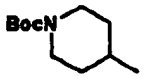
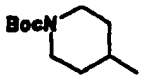
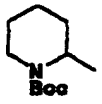
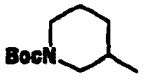
(continued)

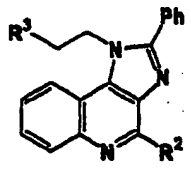
| Example | $R^1$ | B | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 7 | Ph | H | 2 | pale yellow crystals ($CH_2Cl_2$-EtOH)<br>mp,246.5-249°C<br>Elemental analysis for $C_{42}H_{37}ClN_4$<br>Calcd.%: C, 79.68; H, 5.89; N, 8.85<br>Found%: C, 79.55; H, 6.12; N, 8.71 |
| 8 | Ph | H | 3 | colorless crystals (AcOEt)<br>mp,227.5-231°C (decomposition)<br>Elemental analysis for $C_{43}H_{39}ClN_4$-1/4$H_2O$<br>Calcd.%: C, 79.24; H, 6.11; N, 8.60<br>Found%: C, 79.26; H, 6.09; N, 8.55 |

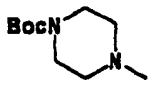
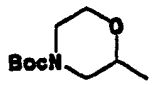
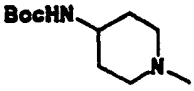
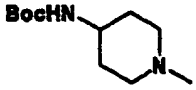


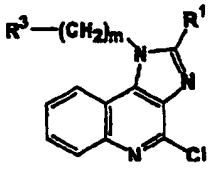
| Example | $R^1$ | B | $R^A$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|---|
| 9 | H | H | Bn | 2 | colorless crystals (AcOEt) mp,124.5-125°C Elemental analysis for $C_{24}H_{25}ClN_4$ Calcd.%: C, 71.19; H, 6.22; N, 13.84 Found%: C, 71.22; H, 5.97; N, 13.79 |
| 10 | Ph | H | Boc | 0 | colorless crystals (AcOEt-MeOH) mp,250-255°C (decomposition) Elemental analysis for $C_{28}H_{27}ClN_4O_2$ Calcd.%: C, 67.45; H, 5.88; N, 12.10 Found%: C, 67.42; H, 5.88; N, 12.02 |
| 11 | H | H | Boc | 2 | colorless crystals (AcOEt) mp,188-189°C Elemental analysis for $C_{22}H_{27}ClN_4O_2$ Calcd.%: C, 63.68; H, 6.56; N, 13.50 Found%: C, 63.45; H, 6.60: N, 13.40 |
| 12 | Ph | Cl | Boc | 2 | colorless crystals (AcOEt) mp,192-193°C Elemental analysis for $C_{28}H_{30}Cl_2N_4O_2$ Calcd.%: C, 64.00; H, 5.75; N, 10.66 Found%: C, 64.04; H, 5.59; N, 10.61 |
| 13 | Ph | Me | Boc | 2 | colorless crystals (AcOEt) mp,182.5-183.5°C Elemental analysis for $C_{29}H_{33}ClN_4O_2$ Calcd.%: C, 68.97; H, 6.59; N, 11.09 Found%: C, 68.91; H, 6.41; N, 11.06 |

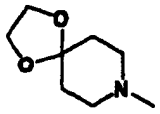
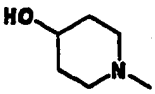
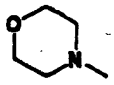
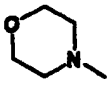
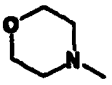


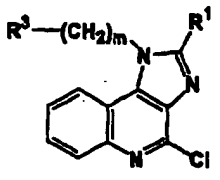
| Example | B | $R^3$ | W | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 14 | MeO |  | CH | colorless crystals (AcOEt)<br>mp,188.5–189.5℃<br>Elemental analysis for $C_{28}H_{33}ClN_4O_2$<br>Calcd.%: C, 68.85; H, 6.38; N, 10.75<br>Found%: C, 68.70; H, 6.42; N, 10.70 |
| 15 | H |  | N | colorless crystals (MeOH)<br>mp,225.5–227.5℃(decomposition)<br>Elemental analysis for $C_{27}H_{30}ClN_5O_2$<br>Calcd.%: C, 65.91; H, 6.15; N, 14.23<br>Found%: C, 65.85; H, 6.21; N, 14.21 |
| 16 | H |  | CH | colorless crystals(AcOEt–n–Heptane)<br>mp,159–161℃<br>Elemental analysis for $C_{28}H_{31}ClN_4O_2$<br>Calcd.%: C, 68.49; H, 6.36; N, 11.41<br>Found%: C, 68.36; H, 6.27; N, 11.37 |
| 17 | H |  | CH | colorless crystals (AcOEt–iso–$Pr_2O$)<br>mp,154.5–156℃<br>Elemental analysis for $C_{28}H_{31}ClN_4O_2$<br>Calcd.%: C, 68.49; H, 6.36; N, 11.41<br>Found%: C, 68.59; H, 6.15; N, 11.38 |
| 18 | H |  | CH | colorless crystals (AcOEt)<br>mp,166.5–167.5℃<br>Elemental analysis for $C_{28}H_{31}ClN_4O_2$<br>Calcd.%: C, 68.49; H, 6.36; N, 11.41<br>Found%: C, 68.50; H, 6.43; N, 11.32 |

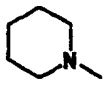
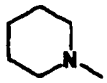
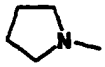
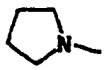


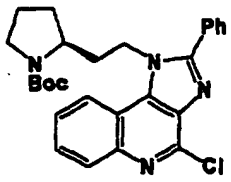
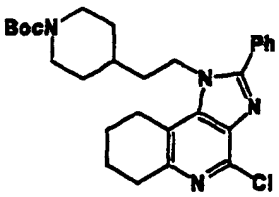
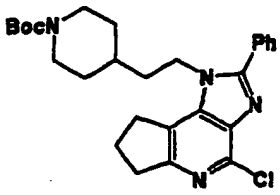
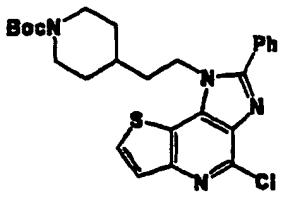
| Example | $R^2$ | $R^3$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 19 | Cl |  | colorless fine needles(AcOEt)<br>mp,186.5–187.5℃<br>Elemental analysis for $C_{27}H_{30}ClN_5O_2$<br>Calcd.%: C, 65.91; H, 6.15; N, 14.23<br>Found%: C, 65.97; H, 6.31; N, 14.18 |
| 20 | Cl |  | colorless crystals (MeOH)<br>mp,195.5–196.5℃<br>Elemental analysis for $C_{27}H_{29}ClN_4O_3$<br>Calcd.%: C, 65.78; H, 5.93; N, 11.36<br>Found%: C, 65.73; H, 5.86; N, 11.38 |
| 21 | Cl |  | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,191.5–192℃<br>Elemental analysis for $C_{28}H_{32}ClN_5O_2$<br>Calcd.%: C, 66.46; H, 6.37; N, 13.84<br>Found%: C, 66.42; H, 6.33; N, 13.69 |
| 22 | Me |  | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,164.5–165℃<br>Elemental analysis for $C_{29}H_{35}N_5O_2$<br>Calcd.%: C, 71.72; H, 7.26; N, 14.42<br>Found%: C, 71.40; H, 7.24; N, 14.28 |

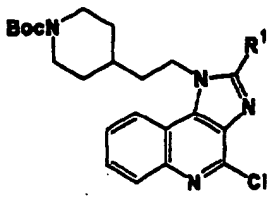


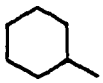
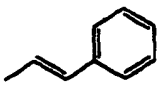
| Example | $R^1$ | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 23 | Ph |  | 2 | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,185-188℃<br>Elemental analysis for $C_{25}H_{25}ClN_4O_2$<br>Calcd.%: C, 66.88; H, 5.61; N, 12.48<br>Found%: C, 66.59; H, 5.63; N, 12.45 |
| 24 | Ph |  | 2 | colorless crystals (iso-PrOH)<br>mp,164-170℃<br>Elemental analysis for $C_{23}H_{23}ClN_4O$<br>Calcd.%: C, 67.89; H, 5.70; N, 13.77<br>Found%: C, 67.62; H, 5.71; N, 13.63 |
| 25 | Ph |  | 2 | pale yellowish brown crystals (AcOEt)<br>mp,182-183℃<br>Elemental analysis for<br>$C_{22}H_{21}ClN_4O \cdot 1/4H_2O$<br>Calcd.%: C, 66.49; H, 5.45; N, 14.10<br>Found%: C, 66.26; H, 5.50; N, 14.03 |
| 26 | H |  | 3 | pale brown crystals (AcOEt)<br>mp,130.5-131.5℃<br>Elemental analysis for $C_{17}H_{19}ClN_4O$<br>Calcd.%: C, 61.72; H, 5.79; N, 16.94<br>Found%: C, 61.72; H, 5.76; N, 16.90 |
| 27 | Ph |  | 3 | pale brown crystals (MeOH)<br>mp,163.5-164.5℃<br>Elemental analysis for $C_{23}H_{23}ClN_4O$<br>Calcd.%: C, 67.89; H, 5.70; N, 13.77<br>Found%: C, 67.91; H, 5.66; N, 13.80 |

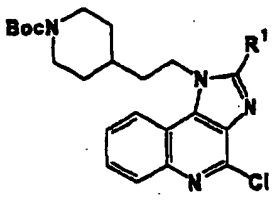


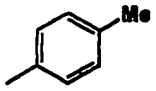
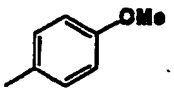
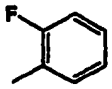
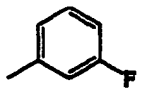
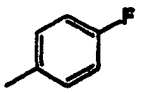
| Example | $R^1$ | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 28 | H |  | 2 | pale brown crystals (iso-$Pr_2O$)<br>mp,105-105.5℃<br>Elemental analysis for $C_{17}H_{18}ClN_4$<br>Calcd.%: C, 64.86; H, 6.08; N, 17.80<br>Found%: C, 64.83; H, 6.11; N, 17.72 |
| 29 | Ph |  | 2 | pale brown crystals (MeOH)<br>mp,226-227℃<br>Elemental analysis for $C_{23}H_{22}ClN_4$<br>Calcd.%: C, 70.67; H, 5.93; N, 14.33<br>Found%: C, 70.44; H, 5.96; N, 14.29 |
| 30 | H |  | 2 | brown crystals<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:1.80-1.90(4H,m),2.58-2.76(4H,m),3.14-3.22(2H,m),4.78-4.91(2H,m),7.68(1H,t,J=8.5Hz),7.72(1H,t,J=8.5Hz),8.13(1H,s),8.22(2H,d,J=8.5Hz)<br>Mass spectrum m/z:300,302($M^+$,3:1) |
| 31 | Ph |  | 2 | pale brown crystals (MeOH)<br>mp,191-192℃<br>Elemental analysis for $C_{22}H_{21}ClN_4$<br>Calcd.%: C, 70.11; H, 5.62; N, 14.87<br>Found%: C, 70.00; H, 5.65; N, 14.86 |

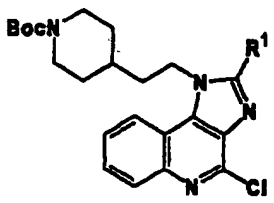
| Example | | Physical properties (Recrystallization solvent) |
|---|---|---|
| 32 |  | colorless amorphous solid<br>NMR spectrum δ (DMSO-$d_6$)ppm:0.99(3H,brs),1.32(3H,brs),1.88(2H,brs),2.13(1H,brs),2.49(9H,s),4.62-4.72(2H,m),7.60-7.67(3H,m),7.74-7.82(4H,m),8.13(1H,dd,J=8,1.5Hz),8.42(1H,d,J=8Hz)<br>IR spectrum ν (KBr)$cm^{-1}$:1690<br>Mass spectrum m/z:476,478($M^+$,3:1)<br>Specific rotation<br>$[\alpha]_D^{20}$ : -60.2° (c=0.1, DMSO) |
| 33 |  | colorless crystals (AcOEt)<br>mp,215-218℃(decomposition)<br>Elemental analysis for $C_{25}H_{25}ClN_4O_2$<br>Calcd.%: C, 67.93; H, 7.13; N, 11.32<br>Found%: C, 67.70; H, 7.17; N, 11.23 |
| 34 |  | colorless crystals (MeOH-Iso-PrOH)<br>mp,185-188℃<br>Elemental analysis for $C_{27}H_{29}ClN_4O_2$<br>Calcd.%: C, 67.42; H, 6.91; N, 11.65<br>Found%: C, 67.31; H, 6.66; N, 11.57 |
| 35 |  | brown crystals (AcOEt)<br>mp,198-200℃<br>Elemental analysis for $C_{25}H_{29}ClN_4O_2S$<br>Calcd.%: C, 62.83; H, 5.88; N, 11.27<br>Found%: C, 62.74; H, 5.83; N, 11.16 |

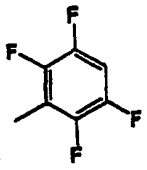
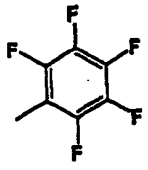
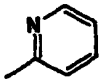
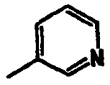
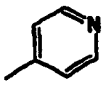


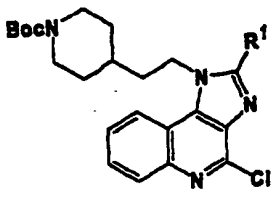
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 36 | Me | pale brown crystals (iso-PrOH)<br>mp,202-203℃<br>Elemental analysis for $C_{23}H_{23}ClN_4O_2$<br>Calcd.%: C, 64.40; H, 6.81; N, 13.06<br>Found%: C, 64.39; H, 7.04; N, 12.95 |
| 37 | n-Bu | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,159.5-160.5℃<br>Elemental analysis for $C_{25}H_{29}ClN_4O_2$<br>Calcd.%: C, 66.30; H, 7.49; N, 11.89<br>Found%: C, 66.16; H, 7.53; N, 11.82 |
| 38 |  | colorless crystals (iso-PrOH)<br>mp,174-175℃<br>Elemental analysis for $C_{28}H_{27}ClN_4O_2 \cdot 1/4H_2O$<br>Calcd.%: C, 67.05; H, 7.54; N, 11.17<br>Found%: C, 67.08; H, 7.47; N, 10.92 |
| 39 | Bn | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,165-166.5℃<br>Elemental analysis for $C_{29}H_{33}ClN_4O_2$<br>Calcd.%: C, 68.97; H, 6.59; N, 11.09<br>Found%: C, 68.93; H, 6.72; N, 10.99 |
| 40 |  | colorless crystals (AcOEt)<br>mp,219-220.5℃(decomposition)<br>Elemental analysis for $C_{30}H_{33}ClN_4O_2 \cdot 1/4H_2O$<br>Calcd.%: C, 69.08; H, 6.47; N, 10.74<br>Found%: C, 69.25; H, 6.41; N, 10.69 |

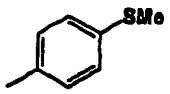
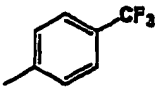
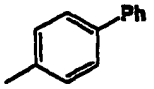
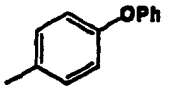


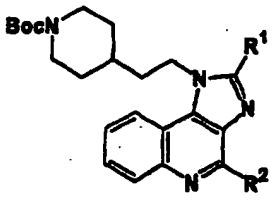
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 41 |  | colorless crystals (MeOH)<br>mp,137-142℃<br>Elemental analysis for $C_{23}H_{23}ClN_4O_2 \cdot 1/2H_2O$<br>Calcd.%: C, 67.76; H, 6.67; N, 10.90<br>Found%: C, 67.82; H, 6.49; N, 10.92 |
| 42 |  | colorless crystals (MeOH)<br>mp,153.5-157℃<br>Elemental analysis for $C_{23}H_{23}ClN_4O_3$<br>Calcd.%: C, 66.85; H, 6.38; N, 10.75<br>Found%: C, 66.84; H, 6.54; N, 10.78 |
| 43 |  | colorless crystals (AcOEt)<br>mp,160-161℃<br>Elemental analysis for $C_{23}H_{20}ClFN_4O_2 \cdot 1/8H_2O$<br>Calcd.%: C, 65.78; H, 5.98; N, 10.96<br>Found%: C, 65.57; H, 5.67; N, 10.94 |
| 44 |  | colorless fine needles<br>(AcOEt-n-Heptane)<br>mp,180-182℃<br>Elemental analysis for $C_{23}H_{20}ClFN_4O_2$<br>Calcd.%: C, 66.07; H, 5.94; N, 11.01<br>Found%: C, 66.10; H, 5.71; N, 11.06 |
| 45 |  | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,126-129.5℃<br>Elemental analysis for $C_{23}H_{20}ClFN_4O_2$<br>Calcd.%: C, 66.07; H, 5.94; N, 11.01<br>Found%: C, 66.06; H, 5.76; N, 11.01 |



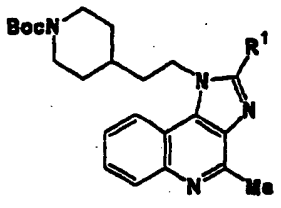
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 46 |  | colorless crystals (iso-PrOH)<br>mp.199.5–200℃<br>Elemental analysis for $C_{28}H_{27}ClF_4N_4O_2$<br>Calcd.%: C, 59.74; H, 4.83; N, 9.95<br>Found%: C, 59.61; H, 4.89; N, 9.90 |
| 47 |  | colorless crystals (iso-PrOH)<br>mp.216.5–217.5℃<br>Elemental analysis for $C_{28}H_{26}ClF_5N_4O_2$<br>Calcd.%: C, 57.89; H, 4.51; N, 9.64<br>Found%: C, 57.88; H, 4.56; N, 9.62 |
| 48 |  | colorless crystals (AcOEt)<br>mp.199.5–200.5℃<br>Elemental analysis for $C_{27}H_{30}ClN_5O_2$<br>Calcd.%: C, 65.91; H, 6.15; N, 14.23<br>Found%: C, 65.77; H, 5.99; N, 14.25 |
| 49 |  | colorless prisms<br>(AcOEt-n-Heptane)<br>mp.182–183℃<br>Elemental analysis for $C_{27}H_{30}ClN_5O_2$<br>Calcd.%: C, 65.91; H, 6.15; N, 14.23<br>Found%: C, 65.95; H, 6.26; N, 14.24 |
| 50 |  | colorless prisms(AcOEt)<br>mp.213–214℃<br>Elemental analysis for $C_{27}H_{30}ClN_5O_2$<br>Calcd.%: C, 65.91; H, 6.15; N, 14.23<br>Found%: C, 65.87; H, 6.20; N, 14.23 |

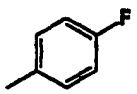
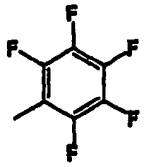
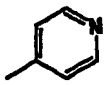
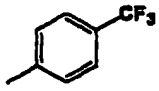


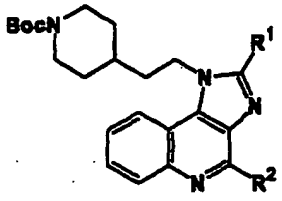
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 51 |  | colorless crystals (MeOH)<br>mp.179–188℃<br>Elemental analysis for $C_{29}H_{33}ClN_4O_2S$<br>Calcd.%: C, 64.85; H, 6.19; N, 10.43<br>Found%: C, 64.82; H, 6.45; N, 10.37 |
| 52 |  | colorless crystals (iso–PrOH)<br>mp.203–203.5℃<br>Elemental analysis for $C_{29}H_{30}ClF_3N_4O_2$<br>Calcd.%: C, 62.31; H, 5.41; N, 10.02<br>Found%: C, 62.24; H, 5.42; N, 9.99 |
| 53 |  | colorless crystals (AcOEt)<br>mp.224–225℃<br>Elemental analysis for $C_{34}H_{33}ClN_4O_2$<br>Calcd.%: C, 72.01; H, 6.22; N, 9.88<br>Found%: C, 72.02; H, 6.21; N, 9.92 |
| 54 |  | colorless crystals (iso–PrOH)<br>mp.197–198℃<br>Elemental analysis for $C_{34}H_{33}ClN_4O_3$<br>Calcd.%: C, 70.03; H, 6.05; N, 9.61<br>Found%: C, 69.83; H, 6.08; N, 9.58 |
| 55 |  | colorless crystals (MeOH)<br>mp.196.5–197℃<br>Elemental analysis for $C_{28}H_{29}ClN_4O_3$<br>Calcd.%: C, 64.93; H, 6.06; N, 11.65<br>Found%: C, 64.83; H, 6.27; N, 11.69 |

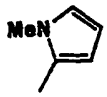


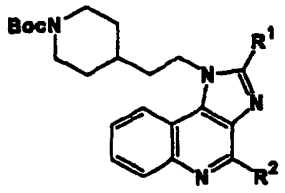
| Example | $R^1$ | $R^2$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 56 |  | Me | pale yellow crystals (iso-PrOH)<br>mp,185.5–186℃<br>Elemental analysis for $C_{27}H_{32}N_4O_3$<br>Calcd.%: C, 70.41; H, 7.00; N, 12.16<br>Found%: C, 70.32; H, 7.19; N, 12.13 |
| 57 |  | Cl | colorless crystals (MeOH)<br>mp,151.5–153℃<br>Elemental analysis for $C_{28}H_{29}ClN_4O_2S$<br>Calcd.%: C, 62.83; H, 5.88; N, 11.27<br>Found%: C, 62.77; H, 6.01; N, 11.24 |
| 58 |  | Me | pale yellow crystals (iso-PrOH)<br>mp,181.5–182.5℃<br>Elemental analysis for $C_{27}H_{32}N_4O_2S$<br>Calcd.%: C, 68.04; H, 6.77; N, 11.75<br>Found%: C, 67.86; H, 6.99; N, 11.63 |
| 59 |  | Cl | colorless crystals (AcOEt)<br>mp,197–198℃<br>Elemental analysis for $C_{28}H_{29}ClN_5O_2S$<br>Calcd.%: C, 60.29; H, 5.67; N, 14.06<br>Found%: C, 59.98; H, 5.54; N, 13.84 |
| 60 |  | Me | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,191–193℃<br>Elemental analysis for $C_{28}H_{31}N_5O_2S$<br>Calcd.%: C, 65.38; H, 6.54; N, 14.66<br>Found%: C, 65.34; H, 6.53; N, 14.43 |

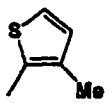
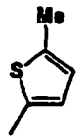
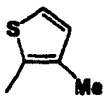
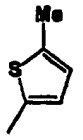


| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 61 |  | yellow amorphous solid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:<br>1.06–1.09(2H,m),1.30–1.40(1H,m),1.40–1.45 ( 2H,m ),1.44(9H,s),1.82–1.90(2H,m),2.55–2.62(2H,m),3.05(3H,s),4.00–4.10(2H,m),4.62(2H,t,J=7.5Hz),7.27–7.30(2H,m),7.61(1H,t,J=7Hz),7.67–7.71(3H,m),8.14(1H,d,J=7.5Hz),8.24(1H,d,J=7.5Hz)<br>IR spectrum $\nu$ (KBr)$cm^{-1}$:1692<br>Mass spectrum m/z:488($M^+$) |
| 62 |  | colorless crystals (AcOEt)<br>mp,195–196℃<br>Elemental analysis for $C_{23}H_{23}F_5N_4O_2$<br>Calcd.%: C, 62.14; H, 5.21; N, 9.99<br>Found%: C, 62.07; H, 5.25; N, 9.94 |
| 63 |  | pale yellow crystals (AcOEt)<br>mp,199.5–200.5℃<br>Elemental analysis for $C_{28}H_{33}N_5O_2$<br>Calcd.%: C, 71.31; H, 7.05; N, 14.85<br>Found%: C, 71.37; H, 7.14; N, 14.83 |
| 64 |  | colorless crystals (MeOH–iso-$Pr_2O$)<br>mp,177.5–179℃<br>Elemental analysis for $C_{30}H_{33}F_3N_4O_2$<br>Calcd.%: C, 66.90; H, 6.18; N, 10.40<br>Found%: C, 66.89; H, 6.08; N, 10.37 |
| 65 |  | pale brown crystals (AcOEt)<br>mp,193–194℃<br>Elemental analysis for $C_{27}H_{33}N_5O_2$<br>Calcd.%: C, 70.56; H, 7.24; N, 15.24<br>Found%: C, 70.61; H, 7.18; N, 15.21 |



| Example | $R^1$ | $R^2$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 66 |  | Cl | colorless crystals (EtOH)<br>mp.240–241℃(decomposition)<br>Elemental analysis for $C_{25}H_{23}ClN_6O_2$<br>Calcd.%: C, 62.43; H, 6.08; N, 17.47<br>Found%: C, 62.49; H, 6.02; N, 17.51 |
| 67 |  | Me | colorless crystals (EtOH)<br>mp.228.5–230℃(decomposition)<br>Elemental analysis for $C_{26}H_{26}N_6O_2$<br>Calcd.%: C, 67.80; H, 7.00; N, 18.25<br>Found%: C, 67.72; H, 6.93; N, 18.24 |
| 68 |  | Me | brown amorphous solid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:1.10–1.20(2H,m),1.48(9H,s),1.40–1.60(3H,m),1.90–1.98(2H,m),2.60–2.70(2H,m),3.04(3H,s),3.86(3H,s),4.05–4.15(2H,m),4.74(2H,t,J=8Hz),6.30(1H,t,J=2.5Hz),6.52(1H,d,J=2.5Hz),6.88(1H,s),7.60(1H,t,J=8Hz),7.67(1H,t,J=8Hz),8.16(1H,d,J=8Hz),8.23(1H,d,J=8Hz)<br>IR spectrum $\nu$ (KBr)$cm^{-1}$:1688<br>Mass spectrum m/z:473($M^+$) |



| Example | $R^1$ | $R^2$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 69 |  | Cl | yellow amorphous solid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:<br>1.05–1.15(2H,m),1.40–1.50(3H,m),1.45(9H,s),1.83–1.90(2H,m),2.32(3H,s),2.60–2.70(2H,m),4.00–4.10(2H,m),4.60–4.65(2H,m),7.06(1H,d,J=5.5Hz),7.51(1H,d,J=5.5Hz),7.68–7.75(2H,m),8.16(1H,d,J=7.5Hz),8.24(1H,d,J=7.5Hz) |
| 70 |  | Cl | pale yellow crystals (EtOH)<br>mp.192–193°C<br>Elemental analysis for $C_{27}H_{31}ClN_4O_2S \cdot 5/4H_2O$<br>Calcd.%: C, 60.77; H, 6.33; N, 10.50<br>Found%: C, 60.82; H, 6.08; N, 10.17 |
| 71 |  | Me | yellow amorphous solid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:<br>1.02–1.08(2H,m),1.44(9H,s),1.44–1.50(3H,m),1.80–1.90(2H,m),2.31(3H,s),2.60–2.70(2H,m),3.05(3H,s),4.00–4.05(2H,m),4.59(2H,t,J=7.5Hz),7.06(1H,d,J=5.5Hz),7.49(1H,d,J=5.5Hz),7.60–7.65(2H,m),8.14(1H,d,J=8Hz),8.23(1H,d,J=8Hz)<br>IR spectrum $\nu$ (KBr)$cm^{-1}$:1688<br>Mass spectrum m/z:490($M^+$) |
| 72 |  | Me | pale yellow crystals (AcOEt)<br>mp.141–142°C<br>Elemental analysis for $C_{28}H_{34}N_4O_2S \cdot 1/4H_2O$<br>Calcd.%: C, 67.92; H, 7.02; N, 11.31<br>Found%: C, 67.86; H, 6.84; N, 11.25 |

Example 73

tert-Butyl 4-[2-(4-chloro-2-hydroxy-1H-imidazo[4,5-c]quinolin-1-yl)-ethyl]-1-piperidinecarboxylate

[0095] To a solution of 0.60 g of tert-butyl 4-(2-(3-amino-2-chloro-4-quinolylamino)-ethyl]-1-piperidinecarboxylate and 0.44 g of triphosgene in 10 ml of 1,2-dichloroethane, 0.41 ml of triethylamine was added dropwise, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution, and extracted with 1,2-dichloroethane. The extract was washed with saturated brine, and dried, and the solvent was evaporated. The residue was washed with diisopropyl ether to give 0.57 g of colorless crystals. Recrystallization from 1,2-dichloroethane gave colorless crystals having the melting point of from 222 to 223°C.

| Elemental analysis for $C_{22}H_{27}ClN_4O_3$ | | | |
|---|---|---|---|
| Calculated % | C, 61.32; | H, 6.32; | N, 13.00 |
| Found % | C, 61.15; | H, 6.34; | N, 13.00 |

Example 74

tert-Butyl 4-[2-[4-chloro-2-(4-methanesulfinylphenyl)-1H-imidazo[4,5-c]-quinolin-1-yl]ethyl]-1-piperidinecarboxylate

[0096] To a suspension of 0.63 g of tert-butyl 4-[2-[4-chloro-2-(4-methylthio-phenyl)-1H-imidazo[4,5-c]quinolin-1-yl] ethyl]-1-piperidinecarboxylate in 18 ml of 1,4-dioxane, a solution of 0.38 g of sodium periodate in 6 ml of water was added dropwise, and the mixture was stirred at 50°C for 13 hours. The reaction solution was concentrated, and the residue was purified by silica gel column chromatography using 1,2-dichloroethane - methanol (10:1) as an eluting solvent to give 0.47 g of a colorless solid. Recrystallization from a mixture of isopropanol and water gave colorless crystals having the melting point of from 183 to 186°C.

| Elemental analysis for $C_{29}H_{33}ClN_4O_3S \cdot 1/4H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 62.46; | H, 6.06; | N, 10.05 |
| Found % | C, 62.33; | H, 5.90; | N, 9.91 |

Example 75

tert-Butyl 4-[2-[4-chloro-2-(4-methanesulfonylphenyl)-1H-imidazo[4,5-c]-quinolin-1-yl]ethyl]-1-piperidinecarboxylate

[0097] To a solution of 0.40 g of tert-butyl 4-[2-[4-chloro-2-(4-methylthiophenyl)-1H-imidazo[4,5 -c]quinolin-1-yl] ethyl]-1-piperidinecarboxylate in 20 ml of 1,2-dichloroethane, 0.40 g of m-chloroperbenzoic acid was added portionwise little by little, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was neutralized with 10% aqueous sodium hydroxide solution, and extracted with 1,2-dichloroethane. The extract was washed with saturated aqueous sodium hydrogencarbonate solution and dried, and then the solvent was evaporated. The residue was washed with a mixture of diisopropyl ether and diethyl ether to give 0.42 g of colorless crystals. Recrystallization from methanol gave colorless crystals having the melting point of from 149 to 156°C.

| Elemental analysis for $C_{29}H_{33}ClN_4O_4S \cdot 1/4H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 60.72; | H, 5.89; | N, 9.77 |
| Found % | C, 60.72; | H, 5.81; | N, 9.67 |

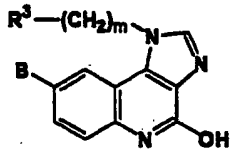
Example 76

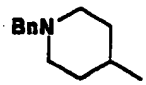
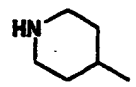
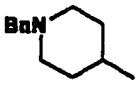
4-Hydroxy-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

[0098] A solution of 871 mg of 4-chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline and 2.5 ml of 6 N hydrochloric acid in 8 ml of 1,4-dioxane was refluxed for 3 hours. The reaction mixture was adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and added with potassium carbonate, and then extracted with 1,2-dichloroethane. The extract was dried, and the solvent was evaporated. The resulting residue was washed with ethyl acetate to give 522 mg of pale brown crystals. Recrystallization from methanol gave pale brown crystals having the melting point of from 242.5 to 244°C.

| Elemental analysis for $C_{23}H_{24}N_4O \cdot 1/4H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 73.28; | H, 6.55; | N, 14.86 |
| Found % | C, 73.32; | H, 6.45; | N, 14.77 |

[0099] In accordance with the method of Example 76, the compounds of Examples 77 through 79 were obtained.



| Example | B | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 77 | Cl |  | 2 | colorless crystals (MeOH)<br>mp.269–280°C (decomposition)<br>Elemental analysis for $C_{24}H_{25}ClN_4O$<br>Calcd.%: C, 68.48; H, 5.99; N, 13.31<br>Found%: C, 68.32; H, 6.07; N, 13.29 |
| 78 | H |  | 1 | colorless crystals [hydrochloride]<br>NMR spectrum δ (DMSO-$d_6$)ppm:<br>1.56(2H,q,J=11.5Hz),1.74(2H,d,J=11.5Hz),2.10–2.25(1H,m),2.79(2H,q,J=11.5Hz),3.24(2H,d,J=11.5Hz),4.54(2H,d,J=7.5Hz),7.29(1H,t,J=8Hz),7.49(1H,d,J=8Hz),7.50(1H,t,J=8Hz),8.00(1H,d,J=8Hz),8.38(1H,s),8.84(1H,brs),8.95(1H,brs),11.62(1H,s)<br>IR spectrum ν (KBr) $cm^{-1}$:3544,3228,1692<br>Mass spectrum m/z:282($M^+$) |
| 79 | H |  | 1 | colorless crystals [hydrochloride]<br>NMR spectrum δ (DMSO-$d_6$)ppm:<br>1.65–1.85(4H,m),2.00–2.15(1H,m),2.84(2H,q,J=12Hz),3.30(2H,d,J=12Hz),4.16(2H,d,J=5Hz),4.51(2H,d,J=7.5Hz),7.27(1H,t,J=8.5Hz),7.40–7.60(7H,m),7.97(1H,d,J=8Hz),8.31(1H,s),10.63(1H,brs),11.58(1H,s)<br>IR spectrum ν (KBr) $cm^{-1}$:3416,1672<br>Mass spectrum m/z:372($M^+$) |

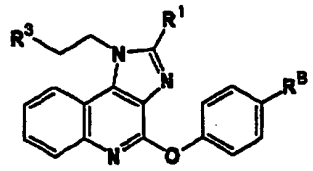
Example 80

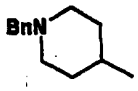
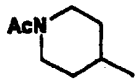
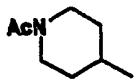
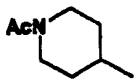
tert-Butyl 4-[2-(4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate

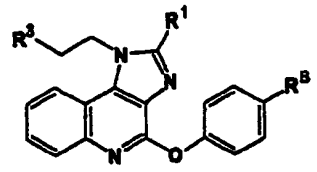
[0100] A mixture of 4.46 g of tert-butyl 4-[2-(4-chloro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate, 10.1 g of phenol and 1.80 g of potassium hydroxide was stirred at 120°C for 7 hours. The reaction mixture was adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed successively with 10% aqueous sodium hydroxide solution and saturated brine, and dried, and then the solvent was evaporated to give a brown liquid. The resulting brown liquid was purified by silica gel column chromatography using ethyl acetate as an eluting solvent to give 3.59 g of a colorless solid. Recrystallization from a mixture of ethyl acetate and n-hexane gave colorless crystals having the melting point of from 130.5 to 132.5°C.

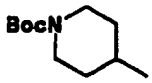
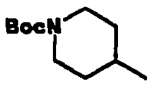
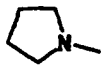
| Elemental analysis for $C_{28}H_{32}N_4O_3$ | | | |
|---|---|---|---|
| Calculated % | C, 71.16; | H, 6.83; | N, 11.86 |
| Found % | C, 71.10; | H, 7.10; | N, 11.69 |

[0101] In accordance with the method of Example 80, the compounds of Examples 81 through 87 were obtained.



| Example | $R^1$ | $R^3$ | $R^B$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 81 | H |  | H | colorless crystals (MeOH)<br>mp.152.5–153.5°C<br>Elemental analysis for $C_{30}H_{28}N_4O$<br>Calcd.%: C, 77.89; H, 6.54; N, 12.11<br>Found%: C, 78.00; H, 6.29; N, 12.05 |
| 82 | H |  | H | colorless crystals (AcOEt–iso–$Pr_2O$)<br>mp.187–189.5°C<br>Elemental analysis for $C_{25}H_{29}N_4O_2$<br>Calcd.%: C, 72.44; H, 6.32; N, 13.52<br>Found%: C, 72.35; H, 6.26; N, 13.42 |
| 83 | H |  | F | colorless crystals ($CH_2Cl_2$–iso–$Pr_2O$)<br>mp.206.5–208°C<br>Elemental analysis for $C_{25}H_{25}FN_4O_2 \cdot 1/8H_2O$<br>Calcd.%: C, 69.07; H, 5.85; N, 12.89<br>Found%: C, 69.11; H, 5.74; N, 12.85 |
| 84 | Ph |  | H | colorless crystals (MeOH–iso–$Pr_2O$)<br>mp.205–207.5°C<br>Elemental analysis for $C_{31}H_{30}N_4O_2 \cdot 1/2H_2O$<br>Calcd.%: C, 74.53; H, 6.25; N, 11.21<br>Found%: C, 74.52; H, 6.37; N, 11.10 |



| Example | $R^1$ | $R^3$ | $R^8$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 85 | H |  | F | colorless crystals (AcOEt-n-Hexane)<br>mp,133.5-135.5℃<br>Elemental analysis for $C_{28}H_{31}FN_4O_3$<br>Calcd.%: C, 68.55; H, 6.37; N, 11.42<br>Found%: C, 68.37; H, 6.47; N, 11.25 |
| 86 | Ph |  | H | colorless crystals (iso-PrOH)<br>mp,207-208℃<br>Elemental analysis for $C_{34}H_{36}N_4O_3$<br>Calcd.%: C, 74.43; H, 6.61; N, 10.21<br>Found%: C, 74.38; H, 6.68; N, 10.14 |
| 87 | H |  | H | pale purple crystals<br>NMR spectrum $\delta$ (DMSO-$d_6$)ppm:<br>1.64-1.72(4H,m),2.55-2.58(4H,m),2.98(2H,t,J=7 Hz),4.80(2H,t,J=7Hz),7.25-7.31(3H,m),7.45-7.49(2H,m),7.53-7.60(2H,m),7.72(1H,d,J=7Hz),8.29(1H,d,J=7Hz),8.37(1H,s)<br>Mass spectrum m/z:358($M^+$) |

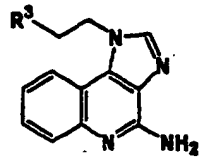
Example 88

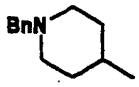
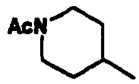
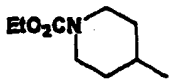
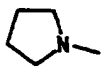
tert-Butyl 4-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate

[0102] A mixture of 4.40 g of tert-butyl 4-[2-(4-phenoxy-1H-imidazo[4,5-c]-quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 34.5 g of ammonium acetate was stirred at 140°C for 3 hours. The reaction mixture was added with water, adjusted to pH 9 with 10% aqueous sodium hydroxide solution, and extracted with methylene chloride. The extract was washed with sarurated brine, and dried, and then the solvent was evaporated. The resulting residue was purified by alumina column chromatography using methylene chloride - methanol (100:1 to 20:1) as eluting solvents, and washed with diisopropyl ether to give 1.88 g of colorless crystals. Recrystallization from ethyl acetate gave colorless crystals having the melting point of from 193 to 193.5°C.

| Elemental analysis for $C_{22}H_{29}N_5O_2$ | | | |
|---|---|---|---|
| Calculated % | C, 66.81; | H, 7.39; | N, 17.71 |
| Found % | C, 66.93; | H, 7.48; | N, 17.66 |

[0103] In accordance with the method of Example 88, the compounds of Examples 89 through 92 were obtained.



| Example | $R^3$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 89 |  | colorless crystals (EtOH)<br>mp,191.5–192°C<br>Elemental analysis for $C_{24}H_{27}N_5$<br>Calcd.%: C, 74.77; H, 7.06; N, 18.17<br>Found%: C, 74.87; H, 7.18; N, 18.06 |
| 90 |  | colorless crystals (MeOH)<br>mp,231.5–232.5°C<br>Elemental analysis for $C_{19}H_{23}N_5O$<br>Calcd.%: C, 67.63; H, 6.87; N, 20.76<br>Found%: C, 67.46; H, 6.79; N, 20.63 |
| 91 |  | colorless crystals (EtOH)<br>mp,166–167°C<br>Elemental analysis for $C_{20}H_{25}N_5O_2$<br>Calcd.%: C, 65.37; H, 6.86; N, 19.06<br>Found%: C, 65.52; H, 6.76; N, 18.83 |
| 92 |  | pale yellow crystals [fumarate]<br>(DMF–iso-$Pr_2O$)<br>mp,195–197°C (decomposition)<br>Elemental analysis for $C_{19}H_{19}N_5 \cdot C_4H_4O_4 \cdot 5/4H_2O$<br>Calcd.%: C, 57.20; H, 6.12; N, 16.68<br>Found%: C, 57.20; H, 6.23; N, 16.53 |

Example 93

tert-Butyl 4-[2-(4-dimethylamino-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)-ethyl]-1-piperidinecarboxylate

[0104] A mixture of 0.69 g of tert-butyl 4-[2-(4-chloro-2-phenyl-1H-imidazo[4,5-c]-quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 7 ml of 50% aqueous dimethylamine solution was stirred in a sealed tube at 80°C of outer temperature for 2 hours. The reaction solution was added with water and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and the solvent was evaporated. The residue was washed successively with isopropanol and diisopropyl ether to give 0.52 g of colorless crystals. Recrystallization from isopropanol gave colorless crystals having the melting point of from 170.5 to 171.5°C.

| Elemental analysis for $C_{30}H_{37}N_5O_2$ | | | |
|---|---|---|---|
| Calculated % | C, 72.12; | H, 7.46; | N, 14.02 |
| Found % | C, 71.95; | H, 7.72; | N, 13.83 |

Example 94

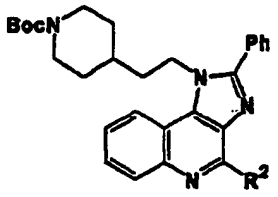
tert-Butyl 4-[2-[4-(4-methylpiperazin-1-yl)-2-phenyl-1H-imidazo[4,5-c]-quinolin-1-yl]ethyl]-1-piperidinecarboxylate

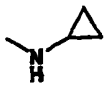
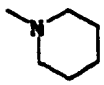
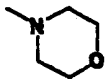
[0105] A mixture of 0.80 g of tert-butyl 4-[2-(4-chloro-2-phenyl-1H-imidazo-[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 1 ml of N-methylpiperazine was stirred at 80°C for 6 hours. The reaction mixture was added with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was dried, and the solvent was evaporated. The residue was purified by alumina column chromatography using ethyl acetate - n-heptane (1:3 to 1:1) as eluting solvents, and washed with a mixture of diisopropyl ether and n-heptane to give 0.74 g

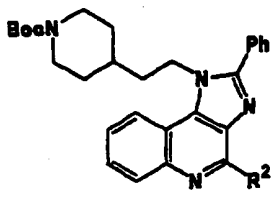
of colorless crystals. Recrystallization from ethyl acetate gave colorless needles having the melting point of from 140 to 141°C.

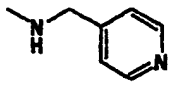
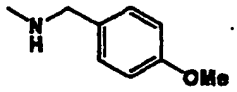
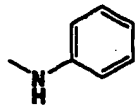
| Elemental analysis for $C_{33}H_{42}N_8O_2$ | | | |
|---|---|---|---|
| Calculated % | C, 71.45; | H, 7.63; | N, 15.15 |
| Found % | C, 71.23; | H, 7.65; | N, 14.99 |

[0106] In accordance with the methods of Examples 93 and 94, the compounds of Examples 95 through 102 were obtained.



| Example | $R^2$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 95 | NHMe | colorless crystals (iso-PrOH)<br>mp,161–162℃<br>Elemental analysis for $C_{29}H_{35}N_5O_2 \cdot 1/2H_2O$<br>Calcd.%: C, 70.42; H, 7.34; N, 14.16<br>Found%: C, 70.31; H, 7.23; N, 13.95 |
| 96 |  | colorless crystals (iso-$Pr_2O$)<br>mp,162–162.5℃<br>Elemental analysis for $C_{31}H_{37}N_5O_2 \cdot 1/2H_2O$<br>Calcd.%: C, 71.51; H, 7.36; N, 13.45<br>Found%: C, 71.73; H, 7.35; N, 13.09 |
| 97 |  | colorless needles (MeOH)<br>mp,171–172℃<br>Elemental analysis for $C_{33}H_{41}N_5O_2$<br>Calcd.%: C, 73.44; H, 7.66; N, 12.98<br>Found%: C, 73.44; H, 7.88; N, 12.93 |
| 98 |  | colorless crystals (iso-PrOH)<br>mp,189–190℃<br>Elemental analysis for $C_{32}H_{39}N_5O_3$<br>Calcd.%: C, 70.95; H, 7.26; N, 12.93<br>Found%: C, 71.22; H, 7.47; N, 12.94 |
| 99 | NHBn | pale brown amorphous solid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:<br>0.99–1.06(2H,m),1.25–1.40(3H,m),1.43(9H,s),1.80–1.90(2H,m),2.50–2.60(2H,m),3.95–4.05(2H,m),4.59(2H,t,J=7.5Hz),4.96(2H,d,J=5.5Hz),6.11(1H,t,J=5.5Hz),7.24–7.28(1H,m),7.30–7.35(3H,m),7.48(2H,d,J=7.5Hz),7.50–7.55(4H,m),7.60–7.65(2H,m),7.94–7.96(2H,m)<br>IR spectrum $\nu$ (KBr) $cm^{-1}$:3436,1690<br>Mass spectrum m/z:561($M^+$) |



| Example | $R^2$ | Physical properties |
|---|---|---|
| 100 |  | pale yellow amorphous solid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:<br>1.00–1.08(2H,m),1.30–1.35(1H,m),1.38–1.42(2H,m),1.43(9H,s),1.83–1.90(2H,m),2.57(2H,brs),3.98(2H,brs),4.61(2H,t,J=7.5Hz),4.99(2H,d,J=6Hz),7.33–7.35(1H,m),7.39(2H,d,J=6Hz),7.51–7.59(4H,m),7.64–7.67(2H,m),7.88–7.89(1H,m),7.96–7.97(1H,m),8.53(2H,d,J=6Hz)<br>IR spectrum $\nu$ (KBr) $cm^{-1}$:3428,1692<br>Mass spectrum m/z:562($M^+$) |
| 101 |  | pale brown amorphous solid<br>NMR spectrum $\delta$ ($CDCl_3$)ppm:<br>0.98–1.06(2H,m),1.25–1.40(3H,m),1.43(9H,s),1.80–1.85(2H,m),2.50–2.60(2H,m),3.79(3H,s),3.90–4.00(2H,m),4.59(2H,t,J=7.5Hz),4.87(2H,d,J=5.5Hz),6.05(1H,brs),6.86(2H,d,J=8.5Hz),7.31(1H,t,J=7.5Hz),7.40(2H,d,J=8.5Hz),7.51–7.60(4H,m),7.60–7.65(2H,m),7.94(2H,d,J=8.5Hz)<br>IR spectrum $\nu$ (KBr) $cm^{-1}$:3432,1692<br>Mass spectrum m/z:591($M^+$) |
| 102 |  | colorless amorphous solid<br>NMR spectrum $\delta$ ($DMSO-d_6$)ppm:<br>0.87(2H,q,J=5Hz),1.20–1.35(3H,m),1.36(9H,s),1.75(2H,q,J=7.5Hz),2.54(2H,t,J=12.5Hz),3.77(2H,d,J=12.5Hz),4.64(2H,t,J=7.5Hz),6.99(1H,t,J=8Hz),7.34(2H,t,J=8Hz),7.44(1H,t,J=7.5Hz),7.56(1H,t,J=7.5Hz),7.60–7.67(3H,m),7.76–7.82(2H,m),7.87(1H,d,J=7.5Hz),8.16(1H,d,J=7.5Hz),8.24(2H,d,J=8Hz),9.03(1H,s)<br>IR spectrum $\nu$ (KBr) $cm^{-1}$:2932,1692<br>Mass spectrum m/z:547($M^+$) |

Example 103

4-Amino-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline trifluoroacetate

[0107] A mixture of 0.30 g of tert-butyl 4-[2-[4-(4-methoxybenzylamino)-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl]ethyl]-1-piperidinecarboxylate and 9 ml of trifluoroacetic acid was stirred at 65°C of outer temperature for 6 hours. The reaction solution was concentrated, and the residue was added with isopropanol. The precipitated crystals were collected by filtration, and washed with diisopropyl ether to give 0.31 g of pale yellow crystals. Recrystallization from a mixture of ethanol and isopropanol gave colorless crystals having the melting point of from 223 to 224°C.

| Elemental analysis for $C_{23}H_{25}N_5 \cdot 2CF_3CO_2H \cdot H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 52.51; | H, 4.73; | N, 11.34 |
| Found % | C, 52.61; | H, 4.45; | N, 11.61 |

Example 104

1-[2-(4-Chloro-2-phenyl-1H-imidazo [4,5-c]quinolin-1-yl)ethyl]-4-piperidinone

**[0108]** A mixture of 0.39 g of 1-[2-(4-chloro-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-4,4-ethylenedioxypiperidine and 4 ml of concentrated sulfuric acid was stirred at room temperature for 30 minutes. The reaction mixture was poured into ice-water, adjusted to pH 11 with 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogencarbonate solution and dried, and then the solvent was evaporated to give 0.42 g of a colorless liquid. The resulting liquid was purified by alumina column chromatography using ethyl acetate - n-heptane (1:1) as an eluting solvent to give 0.32 g of colorless crystals. Recrystallization from isopropanol gave colorless needles having the melting point of from 163 to 165°C.

| Elemental analysis for $C_{23}H_{21}ClN_4O$ | | | |
|---|---|---|---|
| Calculated % | C, 68.23; | H, 5.23; | N, 13.84 |
| Found % | C, 68.26; | H, 5.31; | N, 13.78 |

Example 105

1-[2-(4-Chloro-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-4-piperidinone oxime

**[0109]** A mixture of 0.20 g of 1-[2-(4-chloro-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-4-piperidinone, 0.04 g of hydroxylamine hydrochloride, 0.09 g of sodium acetate and 4 ml of methanol was stirred at room temperature for 1 hour. The reaction solution was concentrated, and the residue was added with aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogencarbonate solution, and dried, and the solvent was evaporated to give 0.25 g of a colorless solid. Recrystallization from ethyl acetate gave colorless crystals having the melting point of from 201 to 207°C (decomposition).

| Elemental analysis for $C_{23}H_{22}ClN_5O \cdot 1/2H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 64.41; | H, 5.40; | N, 16.33 |
| Found % | C, 64.75; | H, 5.32; | N, 16.09 |

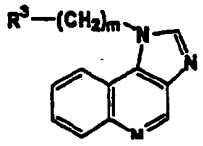
Example 106

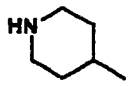
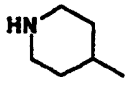
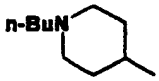
tert-Butyl 4-[2-(2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate

**[0110]** A suspension of 0.80 g of tert-butyl 4-[2-(4-chloro-2-phenyl-1H-imidazo-[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 0.30 g of 5% palladium on carbon in 80 ml of methanol was catalytically hydrogenated at ordinary temperature under atmospheric pressure for 12 hours. After the reaction, the catalyst was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography using ethyl acetate - n-heptane (1:1 to 4:1) as eluting solvents and washed with diisopropyl ether to give 0.49 g of pale yellow crystals. Recrystallization from diisopropyl ether gave colorless crystals having the melting point of from 138 to 139°C.

| Elemental analysis for $C_{28}H_{32}N_4O_2$ | | | |
|---|---|---|---|
| Calculated % | C, 73.66; | H, 7.06; | N, 12.27 |
| Found % | C, 73.46; | H, 7.21; | N, 12.17 |

**[0111]** In accordance with the method of Example 106, the compounds of Examples 107 through 109 were obtained.



| Example | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 107 |  | 1 | colorless crystals [hydrochloride] (MeOH) mp.258–261°C (decomposition) Elemental analysis for $C_{16}H_{16}N_4 \cdot 2HCl \cdot H_2O$ Calcd.%: C, 53.79; H, 6.21; N, 15.68 Found%: C, 53.49; H, 6.14; N, 15.67 |
| 108 |  | 2 | colorless crystals [hydrochloride] (MeOH–$ClCH_2CH_2Cl$) mp.220–233°C (decomposition) Elemental analysis for $C_{17}H_{20}N_4 \cdot 2HCl \cdot 1/2H_2O$ Calcd.%: C, 56.36; H, 6.40; N, 15.46 Found%: C, 56.36; H, 6.18; N, 15.35 |
| 109 |  | 2 | colorless crystals [hydrochloride] (MeOH–iso-$Pr_2O$) mp.225–238°C (decomposition) Elemental analysis for $C_{21}H_{28}N_4 \cdot 2HCl \cdot 1/8H_2O$ Calcd.%: C, 61.27; H, 7.41; N, 13.61 Found%: C, 61.03; H, 7.44; N, 13.50 |

Example 110

4-Chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline hydrochloride and fumarate

[0112] A mixture of 3.64 g of 4-chloro-2-phenyl-1-[2-(N-triphenylmethyl-4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline, 30 ml of methanol and 10 ml of trifluoroacetic acid was stirred at room temperature for 1 hour. The reaction mixture was concentrated, and the residue was washed successively with ethyl acetate and diethyl ether to give pale brown crystals (trifluoroacetate). The resulting crystals were added with ethyl acetate, and extracted with water. The aqueous layer was adjusted to pH 11 with 10% aqueous sodium hydroxide solution, and extracted with a mixture of 1,2-dichloroethane and methanol. The extract was washed with saturated brine, and dried, and then the solvent was evaporated to give 1.74 g of a colorless liquid. A part of the colorless liquid was converted into hydrochloride in a conventional method. Recrystallization from methanol gave colorless crystals having the melting point of from 257 to 265°C (decomposition). In the same manner, fumarate was prepared in a conventional method. Recrystallization from methanol gave colorless crystals having the melting point of from 185.5 to 186.5°C (decomposition).

Hydrochloride:

[0113]

| Elemental analysis for $C_{23}H_{23}ClN_4 \cdot HCl \cdot H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 62.02; | H, 5.88; | N, 12.58 |
| Found % | C, 62.08; | H, 5.77; | N, 12.60 |

Fumarate:

[0114]

| Elemental analysis for $C_{23}H_{23}ClN_4 \cdot C_4H_4O_4 \cdot H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 61.77; | H, 5.57; | N, 10.67 |
| Found % | C, 62.04; | H, 5.40; | N, 10.70 |

Example 111

4-Phenoxy-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline trifluoroacetate

[0115] To a solution of 0.30 g of tert-butyl 4-[2-(4-phenoxy-1H-imidazo[4,5-c]-quinolin-1-yl)ethyl]-1-piperidinecarboxylate in 10 ml of methylene chloride, 1 ml of trifluoroacetic acid was added at room temperature, and the mixture was stirred for 1.5 hours. The reaction solution was concentrated. The resulting pale yellow solid was washed successively with isopropanol and diisopropyl ether to give 0.36 g of colorless crystals. Recrystallization from a mixture of methylene chloride and ethanol gave colorless crystals having the melting point of from 211 to 216°C.

| Elemental analysis for $C_{23}H_{24}N_4O \cdot CF_3CO_2H \cdot 1/8H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 61.44; | H, 5.21; | N, 11.46 |
| Found % | C, 61.26; | H, 5.05; | N, 11.47 |

Example 112

4-Chloro-2-phenyl-1-[2-(1-piperazinyl)ethyl]-1H-imidazo[4,5-c]quinoline methanesulfonate

[0116] To a solution of 1.20 g of tert-butyl 4-[2-(4-chloro-2-phenyl-1H-imidazo-[4,5-c]quinolin-1-yl)ethyl]-1-piperazinecarboxylate in 12 ml of 1,2-dichloroethane, 1.2 ml of methanesulfonic acid was added, and the mixture was stirred at room temperature for 5 minutes. The reaction mixture was added with isopropanol and ethanol, and the precipitated crystals were collected by filtration to give 1.24 g of colorless crystals. Recrystallization from methanol gave colorless crystals having the melting point of from 256 to 270°C (decomposition).

| Elemental analysis for $C_{22}H_{22}ClN_5 \cdot 2CH_3SO_3H$ | | | |
|---|---|---|---|
| Calculated % | C, 49.35; | H, 5.18; | N, 11.99 |
| Found % | C, 49.60; | H, 5.11; | N, 12.16 |

Example 113

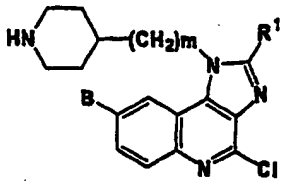
4-Amino-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline hydrochloride

[0117] A mixture of 1.57 g of tert-butyl 4-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-1-piperidinecarboxylate and 40 ml of ethyl acetate solution of hydrogen chloride was stirred at room temperature for 5 hours. The reaction mixture was added with water, adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and extracted with methylene chloride. The extract was dried, and the solvent was evaporated. The resulting residue was washed with ethyl acetate to give 1.01 g of pale brown crystals. The resulting crystals were purified by alumina column chromatography using methylene chloride - methanol (40:1 to 20:1) as eluting solvents, and washed with diisopropyl ether to give colorless crystals. Hydrochloride was prepared in a conventional method. Recrystallization from ethanol gave colorless crystals having the melting point of from 243 to 244°C (decomposition).

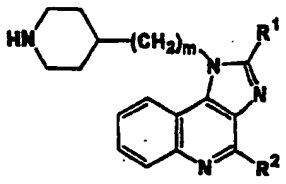
| Elemental analysis for $C_{17}H_{21}N_5 \cdot HCl \cdot 3/4H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 59.12; | H, 6.86; | N, 20.28 |
| Found % | C, 59.10; | H, 6.83; | N, 20.30 |

[0118] In accordance with the methods of Examples 110 through 113, the compounds of Examples 114 through 186

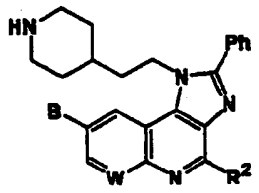
were obtained.



| Example | $R^1$ | B | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 114 | Ph | H | 0 | colorless crystals ($ClCH_2CH_2Cl$-AcOEt)<br>mp,253-256°C (decomposition)<br>Elemental analysis for $C_{21}H_{19}ClN_4$<br>Calcd.%: C, 69.51; H, 5.28; N, 15.44<br>Found%: C, 69.29; H, 5.19; N, 15.27 |
| 115 | H | H | 1 | colorless crystals [hydrochloride]<br>(MeOH-EtOH)<br>mp,273-286°C (decomposition)<br>Elemental analysis for $C_{16}H_{17}ClN_4$-2HCl<br>Calcd.%: C, 51.42; H, 5.12; N, 14.99<br>Found%: C, 51.47; H, 5.08; N, 14.85 |
| 116 | Ph | H | 1 | colorless crystals [fumarate](MeOH)<br>mp,268-271.5°C (decomposition)<br>Elemental analysis for<br>$C_{22}H_{21}ClN_4$-1/2$C_4H_4O_4$-3/2$H_2O$<br>Calcd.%: C, 62.40; H, 5.67; N, 12.13<br>Found%: C, 62.52; H, 5.28; N, 12.15 |
| 117 | H | H | 2 | colorless crystals [hydrochloride]<br>(EtOH)<br>mp,258-267°C (decomposition)<br>Elemental analysis for $C_{17}H_{19}ClN_4$-HCl<br>Calcd.%: C, 58.13; H, 5.74; N, 15.95<br>Found%: C, 57.88; H, 5.46; N, 15.78 |
| 118 | H | Cl | 2 | colorless crystals [trifluoroacetate]<br>(MeOH-iso-$Pr_2O$)<br>mp,204-207.5°C<br>Elemental analysis for<br>$C_{17}H_{18}Cl_2N_4$-$CF_3CO_2H$-1/4$H_2O$<br>Calcd.%: C, 48.78; H, 4.20; N, 11.98<br>Found%: C, 48.76; H, 4.34; N, 11.89 |



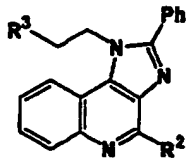
| Example | $R^1$ | $R^2$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 119 | OH | Cl | 2 | pale brown crystals ($ClCH_2CH_2Cl$-MeOH)<br>mp,240-245°C (decomposition)<br>Elemental analysis for<br>$C_{17}H_{19}ClN_4O$-1/2$H_2O$<br>Calcd.%: C, 60.09; H, 5.93; N, 16.49<br>Found%: C, 60.32; H, 5.72; N, 16.41 |
| 120 | Me | Cl | 2 | pale brown crystals [trifluoroacetate] (EtOH)<br>mp,201-202°C<br>Elemental analysis for<br>$C_{18}H_{21}ClN_4$-$CF_3CO_2H$·5/4$H_2O$<br>Calcd.%: C, 51.62; H, 5.31; N, 12.04<br>Found%: C, 51.82; H, 5.12; N, 12.22 |
| 121 | $CF_3$ | Cl | 2 | colorless crystals [trifluoroacetate] (EtOH)<br>mp,233-235°C<br>Elemental analysis for<br>$C_{18}H_{18}ClF_3N_4$-$CF_3CO_2H$<br>Calcd.%: C, 48.35; H, 3.85; N, 11.28<br>Found%: C, 48.31; H, 3.88; N, 11.21 |
| 122 | Ph | H | 2 | colorless crystals [hydrochloride](EtOH)<br>mp,191.5-192.5°C<br>Elemental analysis for<br>$C_{23}H_{24}N_4$-2HCl-$H_2O$<br>Calcd.%: C, 61.74; H, 6.31; N, 12.52<br>Found%: C, 61.69; H, 6.51; N, 12.44 |
| 123 | Ph | Cl | 3 | colorless fine needles[trifluoroacetate] (EtOH)<br>mp,260-263°C (decomposition)<br>Elemental analysis for<br>$C_{24}H_{23}ClN_4 \cdot CF_3CO_2H$<br>Calcd.%: C, 60.17; H, 5.05; N, 10.80<br>Found%: C, 59.94; H, 5.08; N, 10.80 |

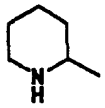
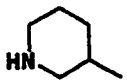
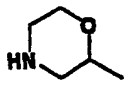
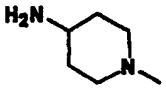
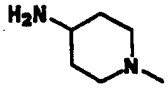


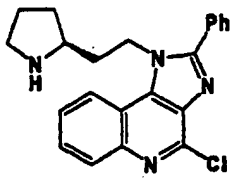
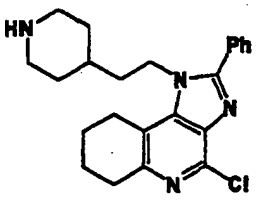
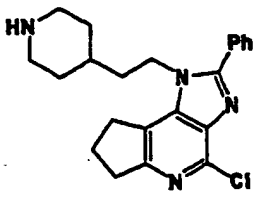
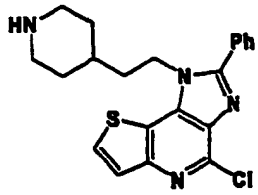

| Example | $R^2$ | B | W | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 124 | Me | H | CH | colorless crystals [hydrochloride](EtOH)<br>mp,199-201 °C<br>Elemental analysis for<br>$C_{24}H_{26}N_4$-HCl-7/2$H_2O$<br>Calcd.%: C, 61.33; H, 7.29; N, 11.92<br>Found%: C, 61.21; H, 7.26; N, 11.80 |

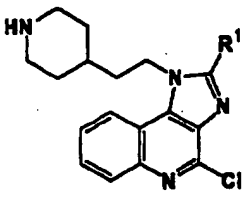
(continued)

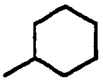
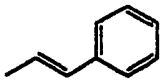
| Example | $R^2$ | B | W | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|
| 125 | Cl | Cl | CH | colorless crystals [trifluoroacetate](MeOH)<br>mp,249-255°C (decomposition)<br>Elemental analysis for<br>$C_{23}H_{22}Cl_2N_4$-$CF_3CO_2H$<br>Calcd.%: C, 55.67; H, 4.30; N, 10.39<br>Found%: C, 55.75; H, 4.00; N, 10.47 |
| 126 | Cl | Me | CH | colorless fine needles[trifluoroacetate]<br>(MeOH)<br>mp,255-262°C (decomposition)<br>Elemental analysis for $C_{24}H_{25}ClN_4$- $CF_3CO_2H$<br>Calcd.%: C, 60.17; H, 5.05; N, 10.80<br>Found%: C, 59.95; H, 5.03; N, 10.79 |
| 127 | Cl | MeO | CH | pale yellow crystals (EtOH)<br>mp,169-170°C<br>Elemental analysis for $C_{24}H_{25}ClN_4O$-$1/2H_2O$<br>Calcd.%: C, 67.05; H, 6.10; N, 13.03<br>Found%: C, 67.32; H, 6.06; N, 13.02 |
| 128 | Cl | H | N | colorless crystals [trifluoroacetate](MeOH)<br>mp,260-268°C (decomposition)<br>Elemental analysis for $C_{22}H_{22}ClN_5$-$CF_3CO_2H$<br>Calcd.%: C, 56.98; H, 4.58; N, 13.84<br>Found%: C, 56.76; H, 4.47; N, 13.82 |

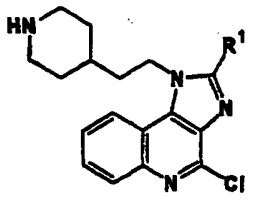


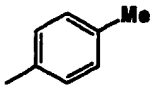
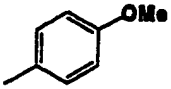
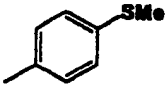
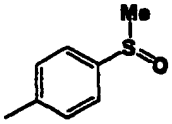
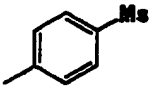
| Example | $R^2$ | $R^3$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 129 | Cl |  | colorless prisms (MeOH)<br>mp.191–193℃<br>Elemental analysis for $C_{23}H_{23}ClN_4$<br>Calcd.%: C, 70.67; H, 5.93; N, 14.33<br>Found%: C, 70.70; H, 6.08; N, 14.28 |
| 130 | Cl |  | colorless crystals (AcOEt)<br>mp.156.5–157.5℃<br>Elemental analysis for $C_{23}H_{23}ClN_4$<br>Calcd.%: C, 70.67; H, 5.93; N, 14.33<br>Found%: C, 70.64; H, 5.92; N, 14.21 |
| 131 | Cl |  | colorless crystals (EtOH)<br>mp.169–171℃<br>Elemental analysis for $C_{23}H_{21}ClN_4O$<br>Calcd.%: C, 67.26; H, 5.39; N, 14.26<br>Found%: C, 67.31; H, 5.55; N, 14.32 |
| 132 | Cl |  | colorless crystals [trifluoroacetate] (iso-PrOH)<br>mp.158–163℃ (decomposition)<br>Elemental analysis for $C_{23}H_{24}ClN_5 \cdot 2CF_3CO_2H \cdot 3/2H_2O$<br>Calcd.%: C, 49.06; H, 4.42; N, 10.60<br>Found%: C, 49.04; H, 4.41; N, 10.73 |
| 133 | Me |  | pale brown crystals (AcOEt)<br>mp.88–89℃<br>Elemental analysis for $C_{24}H_{27}N_5 \cdot H_2O$<br>Calcd.%: C, 71.44; H, 7.24; N, 17.36<br>Found%: C, 71.25; H, 7.23; N, 17.03 |

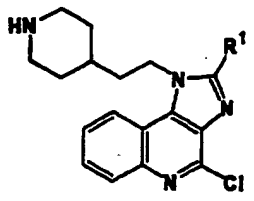
| Example | | Physical properties (Recrystallization solvent) |
|---|---|---|
| 134 |  | colorless fine needles[fumarate](EtOH)<br>mp.261-272℃(decomposition)<br>Elemental analysis for<br>$C_{22}H_{21}ClN_4 \cdot 1/2C_4H_4O_4 \cdot 5/2H_2O$<br>Calcd.%: C, 60.06; H, 5.88; N, 11.67<br>Found%: C, 60.07; H, 5.89; N, 11.60<br>Specific rotation<br>$[\alpha]_D^{20}$: -12.0° (c=0.1, DMSO) |
| 135 |  | colorless crystals [trifluoroacetate]<br>(EtOH)<br>mp.215-221℃(decomposition)<br>Elemental analysis for<br>$C_{23}H_{27}ClN_4 \cdot CF_3CO_2H$<br>Calcd.%: C, 59.00; H, 5.55; N, 11.01<br>Found%: C, 58.85; H, 5.63; N, 11.05 |
| 136 |  | pale brown crystals [trifluoroacetate]<br>(MeOH-iso-PrOH)<br>mp.225-232℃(decomposition)<br>Elemental analysis for<br>$C_{22}H_{23}ClN_4 \cdot CF_3CO_2H$<br>Calcd.%: C, 58.24; H, 5.29; N, 11.32<br>Found%: C, 58.09; H, 5.29; N, 11.32 |
| 137 |  | pale brown crystals [trifluoroacetate]<br>(EtOH)<br>mp.224-224.5℃<br>Elemental analysis for<br>$C_{21}H_{21}ClN_4S \cdot CF_3CO_2H \cdot 3/2H_2O$<br>Calcd.%: C, 51.35; H, 4.68; N, 10.41<br>Found%: C, 51.65; H, 4.32; N, 10.16 |

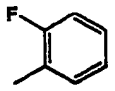
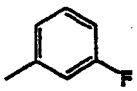
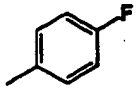
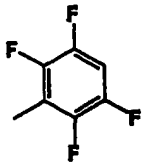
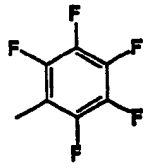


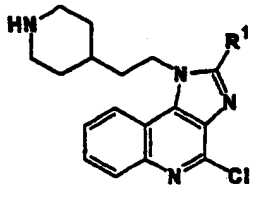
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 138 | n-Bu | colorless crystals (AcOEt)<br>mp,130–131℃<br>Elemental analysis for $C_{21}H_{27}ClN_4$<br>Calcd.%: C, 68.00; H, 7.34; N, 15.10<br>Found%: C, 67.76; H, 7.59; N, 14.96 |
| 139 |  | colorless crystals [trifluoroacetate](EtOH)<br>mp,139–139.5℃<br>Elemental analysis for<br>$C_{23}H_{29}ClN_4 \cdot 3/2CF_3CO_2H \cdot H_2O$<br>Calcd.%: C, 53.29; H, 5.59; N, 9.56<br>Found%: C, 53.23; H, 5.33; N, 9.56 |
| 140 | Bn | pale brown crystals (AcOEt-iso-$Pr_2O$)<br>mp,230–234℃(decomposition)<br>Elemental analysis for $C_{24}H_{25}ClN_4 \cdot 1/4H_2O$<br>Calcd.%: C, 70.40; H, 6.26; N, 13.68<br>Found%: C, 70.41; H, 6.27; N, 13.54 |
| 141 |  | pale yellow crystals [methanesulfonate](MeOH)<br>mp,196–207℃(decomposition)<br>Elemental analysis for<br>$C_{25}H_{29}ClN_4 \cdot 2CH_3SO_3H \cdot H_2O$<br>Calcd.%: C, 51.71; H, 5.62; N, 8.93<br>Found%: C, 51.59; H, 5.42; N, 8.87 |

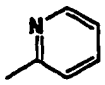
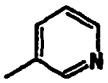
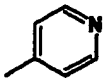
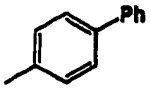
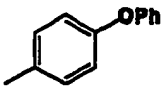


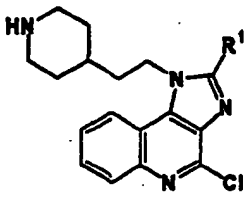
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 142 |  | colorless crystals [fumarate](MeOH)<br>mp.224–229℃(decomposition)<br>Elemental analysis for<br>$C_{24}H_{25}ClN_4 \cdot C_4H_4O_4 \cdot H_2O$<br>Calcd.%: C, 62.39; H, 5.80; N, 10.39<br>Found%: C, 62.46; H, 5.51; N, 10.42 |
| 143 |  | colorless crystals [fumarate](EtOH)<br>mp.213.5–216℃(decomposition)<br>Elemental analysis for<br>$C_{24}H_{25}ClN_4O \cdot C_4H_4O_4 \cdot 1/4H_2O$<br>Calcd.%: C, 62.10; H, 5.49; N, 10.35<br>Found%: C, 61.94; H, 5.45; N, 10.30 |
| 144 |  | colorless crystals [trifluoroacetate]<br>(MeOH-iso-$Pr_2O$)<br>mp.253–257℃(decomposition)<br>Elemental analysis for<br>$C_{24}H_{25}ClN_4S \cdot CF_3CO_2H \cdot 1/2H_2O$<br>Calcd.%: C, 55.76; H, 4.86; N, 10.00<br>Found%: C, 55.67; H, 4.59; N, 9.99 |
| 145 |  | colorless crystals [trifluoroacetate](EtOH)<br>mp.218–225℃(decomposition)<br>Elemental analysis for<br>$C_{24}H_{25}ClN_4OS \cdot CF_3CO_2H$<br>Calcd.%: C, 55.07; H, 4.62; N, 9.88<br>Found%: C, 54.91; H, 4.69; N, 9.77 |
| 146 |  | colorless crystals [trifluoroacetate](MeOH)<br>mp.270–277℃(decomposition)<br>Elemental analysis for<br>$C_{24}H_{25}ClN_4O_2S \cdot CF_3CO_2H$<br>Calcd.%: C, 53.56; H, 4.49; N, 9.61<br>Found%: C, 53.51; H, 4.50; N, 9.62 |

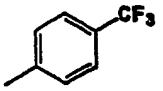


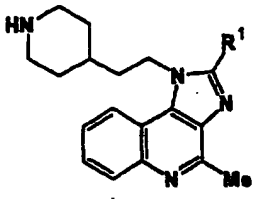
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 147 |  | colorless crystals [fumarate](EtOH)<br>mp.192–198℃(decomposition)<br>Elemental analysis for $C_{23}H_{22}ClFN_4 \cdot C_4H_4O_4 \cdot H_2O$<br>Calcd.%: C, 59.72; H, 5.20; N, 10.32<br>Found%: C, 59.81; H, 5.07; N, 10.33 |
| 148 |  | colorless crystals [fumarate](MeOH–iso–PrOH)<br>mp.184–187℃(decomposition)<br>Elemental analysis for $C_{23}H_{22}ClFN_4 \cdot C_4H_4O_4 \cdot H_2O$<br>Calcd.%: C, 59.72; H, 5.20; N, 10.32<br>Found%: C, 60.00; H, 4.91; N, 10.34 |
| 149 |  | colorless crystals [fumarate](MeOH)<br>mp.204–209℃(decomposition)<br>Elemental analysis for $C_{23}H_{22}ClFN_4 \cdot C_4H_4O_4 \cdot H_2O$<br>Calcd.%: C, 59.72; H, 5.20; N, 10.32<br>Found%: C, 59.53; H, 4.92; N, 10.41 |
| 150 |  | colorless crystals [trifluoroacetate](EtOH)<br>mp.260–263℃(decomposition)<br>Elemental analysis for $C_{23}H_{19}ClF_4N_4 \cdot CF_3CO_2H \cdot H_2O$<br>Calcd.%: C, 50.47; H, 3.73; N, 9.42<br>Found%: C, 50.33; H, 3.53; N, 9.51 |
| 151 |  | colorless crystals [trifluoroacetate](MeOH)<br>mp.259–261℃(decomposition)<br>Elemental analysis for $C_{23}H_{18}ClF_5N_4 \cdot CF_3CO_2H$<br>Calcd.%: C, 50.48; H, 3.22; N, 9.42<br>Found%: C, 50.28; H, 3.28; N, 9.46 |

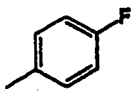
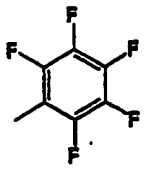
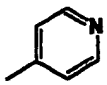
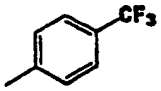


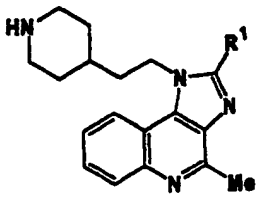
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 152 |  | colorless crystals [methanesulfonate] (EtOH)<br>mp.195–202℃ (decomposition)<br>Elemental analysis for<br>$C_{22}H_{22}ClN_5 \cdot CH_3SO_3H \cdot 5/4H_2O$<br>Calcd.%: C, 54.11; H, 5.63; N, 13.72<br>Found%: C, 54.13; H, 5.45; N, 13.63 |
| 153 |  | colorless crystals [fumarate](MeOH–EtOH)<br>mp.181–185.5℃ (decomposition)<br>Elemental analysis for<br>$C_{22}H_{22}ClN_5 \cdot C_4H_4O_4 \cdot H_2O$<br>Calcd.%: C, 59.37; H, 5.37; N, 13.31<br>Found%: C, 59.37; H, 5.11; N, 13.37 |
| 154 |  | pale yellow fine needles [trifluoroacetate] (EtOH)<br>mp.197.5–204℃ (decomposition)<br>Elemental analysis for<br>$C_{22}H_{22}ClN_5 \cdot CF_3CO_2H \cdot 1/4H_2O$<br>Calcd.%: C, 56.47; H, 4.64; N, 13.72<br>Found%: C, 56.45; H, 4.58; N, 13.72 |
| 155 |  | colorless crystals [trifluoroacetate](EtOH)<br>mp.250–255℃ (decomposition)<br>Elemental analysis for $C_{28}H_{27}ClN_4 \cdot CF_3CO_2H$<br>Calcd.%: C, 64.08; H, 4.86; N, 9.64<br>Found%: C, 63.81; H, 4.92; N, 9.63 |
| 156 |  | colorless crystals [trifluoroacetate](EtOH)<br>mp.144.5–145.5℃<br>Elemental analysis for<br>$C_{28}H_{27}ClN_4O \cdot CF_3CO_2H \cdot 3/2H_2O$<br>Calcd.%: C, 59.66; H, 5.01; N, 8.98<br>Found%: C, 59.44; H, 4.71; N, 9.04 |

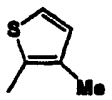
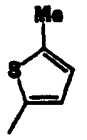


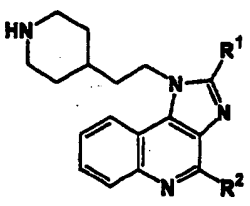
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 157 |  | pale green crystals[trifluoroacetate](EtOH)<br>mp.174-175℃<br>Elemental analysis for<br>$C_{24}H_{22}ClF_3N_4 \cdot CF_3CO_2H \cdot 5/4H_2O$<br>Calcd.%: C, 52.44; H, 4.32; N, 9.41<br>Found%: C, 52.54; H, 4.19; N, 9.53 |
| 158 |  | colorless crystals [trifluoroacetate](MeOH)<br>mp.231-241℃(decomposition)<br>Elemental analysis for<br>$C_{21}H_{21}ClN_4O \cdot CF_3CO_2H \cdot 1/2H_2O$<br>Calcd.%: C, 54.82; H, 4.60; N, 11.12<br>Found%: C, 54.73; H, 4.42; N, 11.21 |
| 159 |  | colorless crystals [trifluoroacetate](EtOH)<br>mp.256-261℃(decomposition)<br>Elemental analysis for<br>$C_{21}H_{21}ClN_4S \cdot CF_3CO_2H \cdot 1/4H_2O$<br>Calcd.%: C, 53.59; H, 4.40; N, 10.87<br>Found%: C, 53.53; H, 4.33; N, 10.90 |
| 160 |  | colorless crystals [trifluoroacetate](MeOH)<br>mp.270-273℃(decomposition)<br>Elemental analysis for<br>$C_{20}H_{21}ClN_6 \cdot CF_3CO_2H \cdot 1/2H_2O$<br>Calcd.%: C, 52.44; H, 4.60; N, 16.68<br>Found%: C, 52.15; H, 4.74; N, 16.95 |
| 161 |  | pale brown crystals [trifluoroacetate]<br>(EtOH-$Et_2O$)<br>mp.203-203.5℃<br>Elemental analysis for $C_{20}H_{20}ClN_5S \cdot CF_3CO_2H$<br>Calcd.%: C, 51.81; H, 4.13; N, 13.68<br>Found%: C, 51.48; H, 4.22; N, 13.52 |

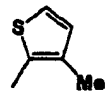
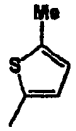
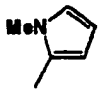
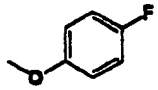


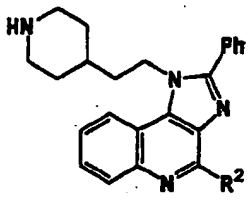
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 162 |  | pale yellow crystals [hydrochloride](iso-PrOH)<br>mp.245-249℃ (decomposition)<br>Elemental analysis for $C_{24}H_{25}FN_4 \cdot 2HCl \cdot 3/4H_2O$<br>Calcd.%: C, 60.70; H, 6.05; N, 11.80<br>Found%: C, 60.81; H, 5.93; N, 11.72 |
| 163 |  | colorless crystals [hydrochloride](EtOH)<br>NMR spectrum $\delta$<br>(DMSO-$d_6$)ppm:1.30-1.40(2H,m),1.55-1.70(1H,m),1.70-1.80(4H,m),2.65-2.80(2H,m),3.10-3.25(2H,m),3.17(3H,s),4.73(2H,t,J=7.5Hz),7.97(1H,t,J=7.5Hz),8.04(1H,t,J=7.5Hz),8.55-8.65(2H,m),8.84(1H,brs),9.06(1H,brs) |
| 164 |  | pale brown crystals (AcOEt)<br>mp.176-177.5℃<br>Elemental analysis for $C_{23}H_{23}N_5$<br>Calcd.%: C, 74.36; H, 6.78; N, 18.85<br>Found%: C, 74.09; H, 6.90; N, 18.69 |
| 165 |  | colorless crystals [hydrochloride]<br>(MeOH-iso-PrOH)<br>mp.>300℃<br>Elemental analysis for $C_{25}H_{25}F_3N_4 \cdot 2HCl \cdot 1/2H_2O$<br>Calcd.%: C, 57.70; H, 5.42; N, 10.77<br>Found%: C, 57.72; H, 5.12; N, 10.79 |
| 166 |  | pale yellow crystals (iso-PrOH)<br>mp.166-167℃<br>Elemental analysis for $C_{22}H_{24}N_4O \cdot H_2O$<br>Calcd.%: C, 69.82; H, 6.92; N, 14.80<br>Found%: C, 69.53; H, 6.97; N, 14.59 |

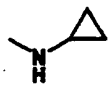


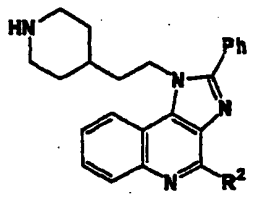
| Example | $R^1$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 167 |  | colorless crystals [hydrochloride]<br>(EtOH)<br>mp.218–219℃<br>Elemental analysis for $C_{21}H_{24}N_6 \cdot 3HCl$<br>Calcd.%: C, 53.68; H, 5.79; N, 17.89<br>Found%: C, 53.63; H, 6.01; N, 17.89 |
| 168 |  | pale yellow crystals [hydrochloride]<br>(MeOH)<br>mp.293–298℃(decomposition)<br>Elemental analysis for<br>$C_{21}H_{23}N_5S \cdot 2HCl \cdot H_2O$<br>Calcd.%: C, 53.84; H, 5.81; N, 14.95<br>Found%: C, 53.59; H, 5.71; N, 14.82 |
| 169 |  | pale yellow crystals [hydrochloride]<br>(EtOH)<br>mp.196–199℃<br>Elemental analysis for<br>$C_{22}H_{24}N_4S \cdot 2HCl \cdot 3H_2O$<br>Calcd.%: C, 52.48; H, 6.41; N, 11.13<br>Found%: C, 52.44; H, 6.68; N, 11.13 |
| 170 |  | pale yellow crystals [trifluoroacetate]<br>(EtOH)<br>mp.228–229℃<br>Elemental analysis for<br>$C_{23}H_{22}N_4S \cdot 3/2CF_3CO_2H \cdot 1/2H_2O$<br>Calcd.%: C, 54.73; H, 5.03; N, 9.82<br>Found%: C, 54.46; H, 4.91; N, 10.00 |
| 171 |  | pale yellow crystals [hydrochloride]<br>(EtOH)<br>mp.274–277℃(decomposition)<br>Elemental analysis for<br>$C_{23}H_{22}N_4S \cdot 2HCl \cdot 5/4H_2O$<br>Calcd.%: C, 56.84; H, 6.33; N, 11.53<br>Found%: C, 56.79; H, 6.11; N, 11.51 |

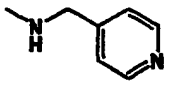
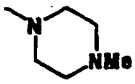
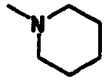
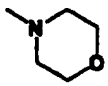


| Example | $R^1$ | $R^2$ | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 172 |  | Cl | colorless crystals [trifluoroacetate] (EtOH) mp.189–190°C Elemental analysis for $C_{22}H_{22}ClN_4S \cdot 3/2CF_3CO_2H$ Calcd.%: C, 51.59; H, 4.24; N, 9.63 Found%: C, 51.54; H, 4.29; N, 9.65 |
| 173 |  | Cl | colorless crystals [trifluoroacetate] (EtOH) mp.194–195°C Elemental analysis for $C_{23}H_{23}ClN_4S \cdot 5/4CF_3CO_2H$ Calcd.%: C, 53.16; H, 4.42; N, 10.12 Found%: C, 53.18; H, 4.39; N, 10.39 |
| 174 |  | Me | pale brown crystals [hydrochloride] (EtOH) mp.245.5–246.5°C Elemental analysis for $C_{23}H_{26}N_4 \cdot 2HCl \cdot 3/2H_2O$ Calcd.%: C, 57.52; H, 6.58; N, 15.24 Found%: C, 57.65; H, 6.33; N, 15.23 |
| 175 |  | Me | pale brown crystals [hydrochloride] (EtOH) mp.224–225°C Elemental analysis for $C_{23}H_{27}N_5 \cdot 2HCl \cdot 5/2H_2O$ Calcd.%: C, 56.21; H, 6.97; N, 14.25 Found%: C, 55.95; H, 6.70; N, 14.23 |
| 176 | H |  | colorless prisms[trifluoroacetate] (EtOH-Iso-$Pr_2O$) mp.189.5–192.5°C Elemental analysis for $C_{22}H_{23}FN_4O \cdot CF_3CO_2H$ Calcd.%: C, 59.52; H, 4.80; N, 11.11 Found%: C, 59.41; H, 4.89; N, 11.16 |



| Example | $R^2$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 177 | OPh | colorless crystals [trifluoroacetate] (EtOH) mp,214.5–215.5℃ Elemental analysis for $C_{28}H_{22}N_4O \cdot CF_3CO_2H \cdot 1/2H_2O$ Calcd.%: C, 65.14; H, 5.29; N, 9.80 Found%: C, 65.40; H, 5.07; N, 9.85 |
| 178 | NHPh | colorless crystals (MeOH–iso–PrOH) mp,191–194℃ Elemental analysis for $C_{29}H_{23}N_5$ Calcd.%: C, 77.82; H, 6.53; N, 15.65 Found%: C, 77.76; H, 6.59; N, 15.56 |
| 179 | NHMe | pale yellow crystals [hydrochloride] (iso–PrOH) mp,209–210℃ Elemental analysis for $C_{24}H_{27}N_5 \cdot 2HCl \cdot 7/4H_2O$ Calcd.%: C, 58.83; H, 6.69; N, 14.29 Found%: C, 58.88; H, 6.51; N, 14.13 |
| 180 | $NMe_2$ | colorless crystals [hydrochloride] (MeOH) mp,205–206.5℃ Elemental analysis for $C_{25}H_{29}N_5 \cdot 2HCl \cdot 5/2H_2O$ Calcd.%: C, 58.02; H, 7.01; N, 13.53 Found%: C, 58.01; H, 7.02; N, 13.50 |
| 181 |  | colorless crystals [hydrochloride] (EtOH) mp,210–212℃ Elemental analysis for $C_{28}H_{25}N_5 \cdot 2HCl \cdot H_2O$ Calcd.%: C, 62.15; H, 6.62; N, 13.94 Found%: C, 61.99; H, 6.44; N, 13.85 |



| Example | $R^2$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 182 | NHBn | colorless crystals [hydrochloride] (iso-PrOH) mp.244-245°C Elemental analysis for $C_{28}H_{31}N_5 \cdot 2HCl \cdot 3/4H_2O$ Calcd.%: C, 65.75; H, 6.35; N, 12.78 Found%: C, 65.81; H, 6.13; N, 12.68 |
| 183 |  | pale yellow crystals [hydrochloride] (EtOH) mp.190-193°C Elemental analysis for $C_{28}H_{30}N_6 \cdot 3HCl \cdot 2H_2O$ Calcd.%: C, 57.29; H, 6.13; N, 13.82 Found%: C, 57.46; H, 5.98; N, 13.77 |
| 184 |  | pale yellow crystals [hydrochloride] (EtOH) mp.231.5-232°C Elemental analysis for $C_{28}H_{34}N_6 \cdot 3HCl \cdot 3/4H_2O$ Calcd.%: C, 58.23; H, 6.72; N, 14.55 Found%: C, 58.12; H, 6.93; N, 14.46 |
| 185 |  | colorless needles [hydrochloride] (EtOH) mp.187-189°C Elemental analysis for $C_{28}H_{33}N_5 \cdot 2HCl \cdot 3/4H_2O$ Calcd.%: C, 63.93; H, 6.99; N, 13.31 Found%: C, 64.05; H, 6.93; N, 13.32 |
| 186 |  | colorless crystals [hydrochloride] (EtOH-iso-PrOH) mp.194-195°C Elemental analysis for $C_{27}H_{31}N_5O \cdot 2HCl \cdot 3/2H_2O$ Calcd.%: C, 59.89; H, 6.70; N, 12.93 Found%: C, 59.72; H, 6.64; N, 12.85 |

Example 187

1-[2-(N-n-Butyl-4-piperidyl)ethyl]-4-chloro-1H-imidazo[4,5-c]quinoline hydrochloride

[0119] To a suspension of 1.20 g of 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline trifluoroacetate and 0.77 g of potassium carbonate in 6 ml of N,N-dimethylformamide, 0.30 ml of n-butyl bromide was added dropwise at room temperature, and the mixture was stirred for 5 hours. The reaction mixture was adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed successively with water

and saturated brine, and dried, and then the solvent was evaporated to give 0.92 g of a pale brown liquid. The resulting liquid was dissolved in tetrahydrofuran. The solution was filtered on silica gel, and the filtrate was concentrated to give 0.87 g of a colorless solid. Hydrochloride was prepared in a conventional method. Recrystallization from a mixture of methanol and ethyl acetate gave colorless crystals having the melting point of from 144 to 158°C.

| Elemental analysis for $C_{21}H_{27}ClN_4 \cdot 2HCl \cdot 1/2H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 55.70; | H, 6.68; | N, 12.37 |
| Found % | C, 55.80; | H, 6.65; | N, 12.44 |

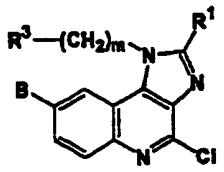
Example 188

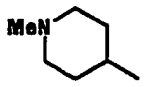
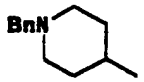
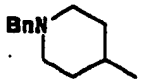
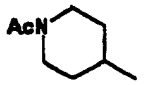
1-[2-(N-Acetyl-4-piperidyl)ethyl]-4-chloro-1H-imidazo[4,5-c]quinoline

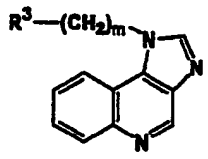
**[0120]** To a solution of 0.60 g of 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline trifluoroacetate in 4 ml of pyridine, 2 ml of acetic anhydride was added, and the mixture was stirred at room temperature for 1 hour. After the reaction, the solvent was evaporated. The residue was added with isopropanol and diisopropyl ether, and the precipitated crystals were collected by filtration, and washed with diisopropyl ether to give 0.45 g of colorless crystals. Recrystallization from a mixture of methylene chloride and diisopropyl ether gave colorless crystals having the melting point of from 183 to 186.5°C.

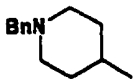
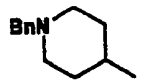
| Elemental analysis for $C_{19}H_{21}ClN_4O$ | | | |
|---|---|---|---|
| Calculated % | C, 63.95; | H, 5.93; | N, 15.70 |
| Found % | C, 63.81; | H, 5.87; | N, 15.61 |

**[0121]** In accorcance with the methods of Examples 187 and 188, the compounds of Examples 189 through 194 were obtained.



| Example | $R^1$ | B | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|---|---|
| 189 | Ph | H |  | 2 | colorless crystals (iso-PrOH)<br>mp.167-168℃<br>Elemental analysis for $C_{24}H_{25}ClN_4$<br>Calcd.%: C, 71.19; H, 6.22; N, 13.84<br>Found%: C, 71.00; H, 6.18; N, 13.56 |
| 190 | H | Cl |  | 2 | colorless crystals [hydrochloride] (EtOH)<br>mp.235-246℃ (decomposition)<br>Elemental analysis for $C_{24}H_{24}Cl_2N_4 \cdot HCl \cdot 1/4H_2O$<br>Calcd.%: C, 60.01; H, 5.35; N, 11.66<br>Found%: C, 60.01; H, 5.62; N, 11.67 |
| 191 | H | H |  | 1 | colorless crystals [hydrochloride] (EtOH)<br>mp.248-257℃ (decomposition)<br>Elemental analysis for $C_{23}H_{23}ClN_4 \cdot HCl \cdot 1/4H_2O$<br>Calcd.%: C, 63.96; H, 5.72; N, 12.97<br>Found%: C, 63.98; H, 5.80; N, 12.93 |
| 192 | Ph | H |  | 2 | colorless crystals ($CH_2Cl_2$-iso-$Pr_2O$)<br>mp.154.5-160℃<br>Elemental analysis for $C_{25}H_{25}ClN_4O \cdot 1/8H_2O$<br>Calcd.%: C, 69.00; H, 5.85; N, 12.87<br>Found%: C, 68.78; H, 5.78; N, 12.71 |



| Example | $R^3$ | m | Physical properties (Recrystallization solvent) |
|---|---|---|---|
| 193 |  | 1 | colorless crystals [hydrochloride] (MeOH-iso-$Pr_2O$) mp.269-280°C (decomposition) Elemental analysis for $C_{23}H_{24}N_4 \cdot 2HCl \cdot 3/4H_2O$ Calcd.%: C, 62.37; H, 6.26; N, 12.65 Found%: C, 62.36; H, 6.45; N, 12.60 |
| 194 |  | 2 | colorless crystals [hydrochloride] (MeOH-iso-$Pr_2O$) mp.150-156°C (decomposition) Elemental analysis for $C_{24}H_{28}N_4 \cdot 2HCl \cdot 1/2H_2O$ Calcd.%: C, 63.71; H, 6.46; N, 12.38 Found%: C, 63.90; H, 6.68; N, 12.11 |

Example 195

4-Chloro-1-[2-[N-(4-fluorophenylsulfonyl)-4-piperidyl]ethyl]-1H-imidazo-[4,5-c]quinoline

**[0122]** To a suspension of 0.50 g of 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline trifluoroacetate and 0.32 g of potassium carbonate in 2 ml of N,N-dimethylformamide, a solution of 0.23 g of p-fluorobenzenesulfonyl chloride in 3 ml of N,N-dimethylformamide was added dropwise at room temperature, and the mixture was stirred for 5 hours. The reaction mixture was adjusted to pH 10 with 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried, and then the solvent was evaporated to give 0.35 g of a colorless solid. Recrystallization from a mixture of methanol, ethanol and water gave colorless crystals having the melting point of from 175 to 178.5°C.

| Elemental analysis for $C_{23}H_{22}ClFN_4O_2S$ | | | |
|---|---|---|---|
| Calculated % | C, 58.41; | H, 4.69; | N, 11.85 |
| Found % | C, 58.43; | H, 4.52; | N, 11.88 |

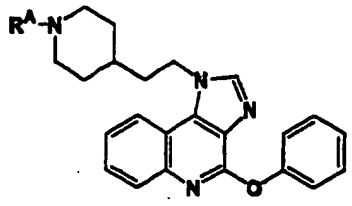
Example 196

1-[2-(N-Methanesulfonyl-4-piperidyl)ethyl]-4-phenoxy-1H-imidazo[4,5-c]-quinoline

**[0123]** To a solution of 1.00 g of 4-phenoxy-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline trifluoroacetate and 0.57 ml of triethylamine in 10 ml of methylene chloride, 0.16 ml of methanesulfonyl chloride was added dropwise at room temperature, and the mixture was stirred for 1.5 hours. The reaction mixture was added with water, and extracted with methylene chloride. The extract was washed with water, and dried, and then the solvent was evaporated to give a colorless liquid. The resulting colorless liquid was solidified with ethyl acetate, and the solid was washed with diethyl ether to give 0.80 g of colorless crystals. Recrystallization from a mixture of methylene chloride and ethyl acetate gave colorless crystals having the melting point of from 173.5 to 176°C.

| Elemental analysis for $C_{24}H_{26}N_4O_3S$ | | | |
|---|---|---|---|
| Calculated % | C, 63.98; | H, 5.82; | N, 12.44 |
| Found % | C, 64.01; | H, 5.96; | N, 12.28 |

**[0124]** In accordance with the method of Example 196, the compounds of Examples 197 through 199 were obtained.



| Example | $R^A$ | Physical properties (Recrystallization solvent) |
|---|---|---|
| 197 | Ts | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,201.5-202°C<br>Elemental analysis for $C_{30}H_{30}N_4O_3S$<br>Calcd.%: C, 68.42; H, 5.74; N, 10.64<br>Found%: C, 68.46; H, 5.83; N, 10.53 |
| 198 | $EtO_2C$ | colorless crystals (AcOEt-iso-$Pr_2O$)<br>mp,132-133°C<br>Elemental analysis for $C_{26}H_{28}N_4O_3$<br>Calcd.%: C, 70.25; H, 6.35; N, 12.60<br>Found%: C, 70.13; H, 6.34; N, 12.50 |
| 199 | $BnO_2C$ | yellow liquid<br>NMR spectrum δ ($CDCl_3$)ppm:<br>1.31 (2H,brs),1.50-1.70(1H,m),1.78(2H,brs),2.00(2H,q,J= 7.5Hz),2.81(2H,brs),4.23(2H, brs),4.63(2H,t,J=7.5Hz),5.1 3(2H,s),7.25(1H,t,J=7Hz),7.30-7.40(5H,m),7.39(2H,d,J= 7Hz), 7.44(2H,t,J=7Hz),7.50(1H,td,J=8.5,1Hz),7.57(1H,t d,J=8.5,1Hz),7.90(1H,dd,J=8.5,1Hz), 7.94(1H,s),8.04(1H, dd,J=8.5,1Hz)<br>IR spectrum ν (liq.) $cm^{-1}$:1698<br>Mass spectrum m/z:506($M^+$) |

Example 200

4-[2 -(4-Amino-1H-imidazo [4,5-c]quinolin-1-yl)ethyl]-N-methyl-1-piperidine-carbothioamide

**[0125]** A suspension of 0.50 g of 4-amino-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]-quinoline and 0.37 g of methyl-isothiocyanate in 10 ml of methylene chloride was stirred at room temperature for 1 hour, and then the precipitated crystals were collected by filtration to give 0.56 g of colorless crystals. Recrystallization from a mixture of methylene chloride and methanol gave colorless crystals having the melting point of from 216 to 218°C.

| Elemental analysis for $C_{19}H_{24}N_8S \cdot 1/2H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 60.45; | H, 6.67; | N, 22.26 |
| Found % | C, 60.79; | H, 6.66; | N, 21.97 |

**[0126]** In accordance with the method of Example 200, the compound of Example 201 was obtained.

Example 201

4-[2-(4-Chloro-2-phenyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-N-methyl-1-piperidinecarbothioamide

**[0127]**

Appearance: colorless crystals
Recrystallization solvent: methanol
mp: 215-220°C (decomposition)

| Elemental analysis for $C_{25}H_{26}ClN_5S$ | | | |
|---|---|---|---|
| Calculated % | C, 64.71; | H, 5.65; | N, 15.09 |
| Found % | C, 64.80; | H, 5.62; | N, 14.96 |

Example 202

1-[2 -(1-Amidino-4-piperidyl)ethyl]-4-chloro-2-phenyl-1H-imidazo[4,5-c]-quinoline hydrochloride

[0128] A solution of 0.75 g of 4-chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo-[4,5-c]quinoline, 0.40 g of 1H-pyrazole-1-carboxyamidine hydrochloride and 0.39 ml of triethylamine in 5 ml of N,N-dimethylformamide was stirred at room temperature for 19 hours. The reaction solution was concentrated and the residue was added with ethanol, and then the precipitated crystals were collected by filtration to give 0.51 g of colorless crystals. Recrystallization from ethanol gave colorless crystals having the melting point of from 270 to 273°C (decomposition).

| Elemental analysis for $C_{24}H_{25}ClN_6 \cdot HCl \cdot 1/2H_2O$ | | | |
|---|---|---|---|
| Calculated % | C, 60.25; | H, 5.69; | N, 17.57 |
| Found % | C, 60.47; | H, 5.61; | N, 17.36 |

[0129] As an example of the excellent effects of the compounds according to the present invention, experimental results of inhibitory actions against production of TNF- α and IL-1β in human cells will be shown below.

1. Preparation of blood cells for culture

[0130] About 50 mL of whole blood was collected from adult healthy volunteers by venepuncture into a plastic tube which containing 170 µL of Novo-heparin 1000 (Novo-Nordisk A/S). Then, PBMCs (Peripheral Blood Mononuclear Cells) were prepared using a cell separation tube, LeucoPREP™ (Becton Dickinson), and cultured with RPMI-1640 medium (Nissui Pharmaceutical Co.) containing 2 mM L -glutamine (Life Technologies), 2.5 U/ml penicillin-2.5 µg/mL streptomycin solution (Life Technologies) supplemented with 10% fetal calf serum (Intergen Company) at $1x10^6$ cells/mL.

2. Preparation of test compounds

[0131] Test compounds were dissolved in distilled ultra-pure water, dimethyl sulfoxide, or 0.1 N hydrochloric acid at 20 µM, and then sequentially diluted with saline and used. The compounds were examined at concentrations ranging from $10^{-10}$ M to $10^{-5}$ M.

3. Treatment of cells with medicaments

[0132] 10 µL of 1 µg/mL lipopolysaccharide (LPS) was added to a 96-well (flat bottom) plate for cell culture, MicroTest III ™ tissue culture plate (Becton Dickinson), containing 180 µL of the PBMCs in the aforementioned medium. After 30 minutes, 10 µL of the solution of the test compound or the solvent was further added to each well, and the plate was covered with a plastic lid and incubated at 37°C for 16 hours in an atmosphere of 5% $CO_2$.

4. Determination of human TNF-a and human IL-1β

[0133] An enzyme immunoassay by the sandwich method was performed to determine the human TNF- α and human IL-1β in the culture supernatant. The anti-cytokine antibody (the first-antibody) was diluted and placed in a 96-well microtiter plates for coating. After the wells were washed, the culture supernatant was appropriately diluted, and then added to each well and incubated. Then the second-antibody against cytokine and the third-antibody against the second-antibody were successively added while applying washing processes between the operations. After the final washing process, a tetramethylbenzidine solution (DAKO) was added to each well to start the coloring reaction. The coloring reaction was quenched with 1 N sulfuric acid, and then the absorbance at 450 nm of each well was measured by a microplate reader, M-Vmax™ (Molecular Devices). The concentrations of the cytokines were determined by quantification software, Softmax™ (Molecular Devices), in comparison with the calibration curves obtained by using the re-

combinant cytokines as the standards. For determination of human TNF-α, monoclonal anti-human TNF-α (ENDOGEN), polyclonal rabbit anti-human TNF-α (Pharma Biotechnologie Hannover), peroxidase conjugated donkey anti-rabbit IgG (Jackson ImmunoRes. Labs.), and recombinant human TNF-α (INTERGEN Company) were used for the first-, second- and third-antibodys and the standard for the calibration curve, respectively. For determination of human IL-1β, monoclonal anti-human IL-1β (Cistron), polyclonal sheep anti-human IL-1β (Biogenesis), HRP conjugated donkey anti-goat IgG (Chemicon International), and recombinant human IL-1β (R&D Systems) were used for the first-, second- and third-antibodys and the standard for the calibration curve, respectively.

**[0134]** In both cases for TNF- α and IL-1 β, the activities of each test compound are shown as percentages (%) of the amount of the cytokine induced by treatment with LPS together with the test compound against the amount of the cytokine induced by treatment solely with LPS.

**[0135]** Results are shown in tables 1 and 2.

Table 1:

| Inhibitory action against TNF- α production in human cells | | | | | |
|---|---|---|---|---|---|
| Compounds | Administered concentration (μmol/L) | | | | |
| | 0.001 | 0.01 | 0.10 | 1.0 | 10 |
| Example 89 | 91 | 86 | 90 | 84 | 17 |
| Example 110 | 80 | 77 | 26 | 1 | 0 |
| Example 113 | 68 | 81 | 86 | 69 | 29 |
| Example 117 | 117 | 77 | 71 | 24 | 0 |
| Example 118 | 79 | 91 | 88 | 51 | 3 |
| Example 121 | 81 | 91 | 49 | 0 | 0 |

Table 2:

| Inhibitory action against IL-1 β production in human cells | | | | | |
|---|---|---|---|---|---|
| Compounds | Administered concentration (μmol/L) | | | | |
| | 0.001 | 0.01 | 0.10 | 1.0 | 10 |
| Example 89 | 112 | 102 | 96 | 63 | 0 |
| Example 110 | 119 | 105 | 85 | 64 | 14 |
| Example 113 | 104 | 109 | 116 | 96 | 30 |
| Example 117 | 119 | 108 | 111 | 72 | 8 |
| Example 118 | 96 | 106 | 102 | 59 | 0 |
| Example 121 | 102 | 108 | 87 | 24 | 0 |

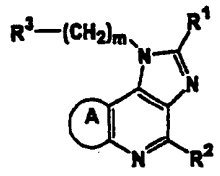
**[0136]** These results clearly indicate that the compounds of the present invention have excellent inhibitory actions against production of TNF and IL-1.

## Industrial Applicability

**[0137]** The compounds of the present invention have excellent inhibitory actions against production of TNF or IL-1 and are extreamely useful as preventive or therapeutic agents of diseases mediated by these cytokines.

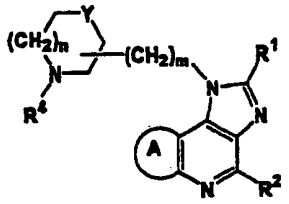
## Claims

1. A 1H-imidazopyridine derivative represented by the following general formula or a salt thereof:



wherein $R^1$ represents hydrogen atom, hydroxyl group, an alkyl group which may have one or more substituents, a cycloalkyl group which may be substituted, a styryl group which may be substituted, or an aryl group which may have one or more substitutents; $R^2$ represents hydrogen atom, an alkyl group, a halogen atom, hydroxyl group, an amino group which may have one or two substituents, a cyclic amino group which may be substituted, or a phenoxy group which may be substituted; ring A represents a homocyclic or a heterocyclic ring which may be substituted with one or more alkyl groups, alkoxyl groups, or halogen atoms; $R^3$ represents a saturated nitrogen-containing heterocyclic group which may be substituted; and m represents an integer of from 0 to 3; provided when $R^3$ represents unsubstituted piperidino group, at least one of $R^1$ and $R^2$ is not hydrogen atom.

2. A 1H-imidazopyridine derivative represented by the following general formula or a salt thereof:



wherein $R^1$ represents hydrogen atom, hydroxyl group, an alkyl group which may have one or more substituents, a cycloalkyl group which may be substituted, a styryl group which may be substituted, or an aryl group which may have one or more substitutents; $R^2$ represents hydrogen atom, an alkyl group, a halogen atom, hydroxyl group, an amino group which may have one or two substituents, a cyclic amino group which may be substituted, or a phenoxy group which may be substituted; ring A represents a homocyclic or heterocyclic ring which may be substituted with one or more alkyl groups, alkoxyl groups, or halogen atoms; m represents an integer of from 0 to 3; $R^4$ represents hydrogen atom, an alkyl group, benzyl group, triphenylmethyl group, an alkanoyl group which may be substituted, an alkoxycarbonyl group, benzyloxycarbonyl group, a thiocarbamoyl group which may be substituted, an alkanesulfonyl group, a benzenesulfonyl group which may be substituted, or amidino group; Y represents methylene group, oxygen atom, sulfur atom, nitrogen atom, a group represented by NH, or a single bond; and n represents an integer of from 0 to 2.

3. The compound or the salt thereof according to claim 1 or claim 2, wherein the ring A is benzene ring or thiophene ring.

4. A medicament which comprises as an active ingredient the 1H-imidazopyridine derivative or a pharmacologically acceptable salt thereof according to claim 1 or claim 2.

5. The medicament according to claim 4 which is used for preventive or therapeutic treatment of a disease in which a cytokine is mediated.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/04381

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl[6] C07D471/04, C07D471/14, C07D491/113, C07D495/14, A61K31/435, A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl[6] C07D471/04, C07D471/14, C07D491/113, C07D495/14, A61K31/435, A61K31/47

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO, 9830562, A (Terumo Kabushiki Kaisha), 16 July, 1998 (16.07.98), & EP, 894797, A | 1-5 |
| A | JP, 09208584, A (Terumo Kabushiki Kaisha), 12 August, 1997 (12.08.97), (Family: none) | 1-5 |
| A | US, 5389640, A (Minnesota Mining and MFG. Co.), 14 February, 1995 (14.02.95), & EP, 872478, A | 1-5 |
| A | US, 5352784, A (Minnesota Mining and MFG. Co.), 04 October, 1994 (04.10.94), & EP, 708773, A & JP, 09500628, A | 1-5 |
| A | J. Interferon Res. (1994), 14, P. 81-85 | 1-5 |
| A | EP, 459505, A (Kyowa Hakko Kogyo Co., Ltd.), 04. December, 1991 (04.12.91), & JP, 04226985, A | 1-5 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 08 November, 1999 (08.11.99) | 16 November, 1999 (16.11.99) |
| Name and mailing address of the ISA/ Japanese Patent Office | Authorized officer |
| Facsimile No. | Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1992)

## INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/04381

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US, 4689338, A (Riker Laboratories, Inc.), 16 July, 1998 (16.07.98), (Family: none) | 1-5 |
| A | EP, 145340, A (Riker Laboratories, Inc.), 19 June, 1985 (19.06.85), & JP, 60123488, A & US, 4698348, A | 1-5 |
| A | HU, 34479, A (Egypt Gyogyszervegyeszeti Gyar), 28 March, 1985 (28.03.85), (Family: none) | 1-5 |
| A | J. Med. Chem. (1968), 11(1), P. 87-92 | 1-5 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

(19)日本国特許庁（JP）　(12)公開特許公報（A）　(11)特許出願公開番号

特開平9－208584

(43)公開日　平成9年(1997)8月12日

| (51)Int.Cl.⁶ | 識別記号 | 庁内整理番号 | FI | | 技術表示箇所 |
|---|---|---|---|---|---|
| C07D 471/04 | 107 | | C07D 471/04 | 107E | |
| A61K 31/445 | ABF | | A61K 31/445 | ABF | |
| | ADA | | | ADA | |
| | AEM | | | AEM | |
| C07D 215/46 | | | C07D 215/46 | | |

審査請求　未請求　請求項の数10　OL　（全 18 頁）

(21)出願番号　特願平8－13113

(22)出願日　平成8年(1996)1月29日

(71)出願人　000109543
テルモ株式会社
東京都渋谷区幡ヶ谷２丁目44番１号

(72)発明者　藤波　亮一
神奈川県足柄上郡中井町井ノ口1500番地
テルモ株式会社内

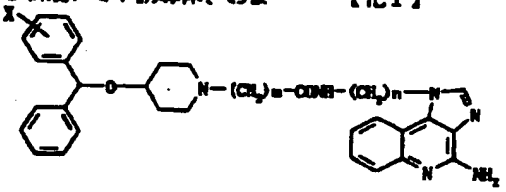
(72)発明者　石井　竹夫
神奈川県足柄上郡中井町井ノ口1500番地
テルモ株式会社内

(72)発明者　西田　仁
神奈川県足柄上郡中井町井ノ口1500番地
テルモ株式会社内

最終頁に続く

(54)【発明の名称】　アミド誘導体、およびそれを含有する医薬製剤、および合成中間体

(57)【要約】
【課題】抗ヒスタミン効果及び好酸球浸潤抑制効果を有し、即時型及び遅発型のアレルギー反応を強く抑え、特にアトピー性皮膚炎の治療に有効な新規化合物を得る。
【解決手段】下記式で示される新規アミド誘導体、およびそれを含有する医薬製剤、および新規アミド誘導体の合成中間体。式中、Xは水素原子またはハロゲン原子を示し、mは１から９の整数を、nは２から１２の整数を示す。
【化１】

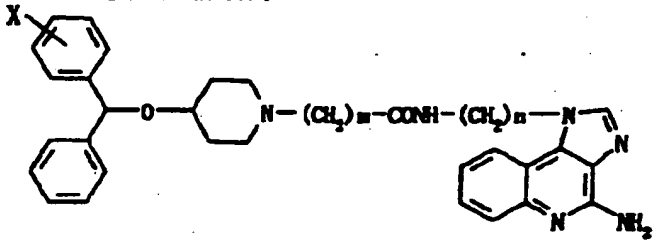


(I)

1

【特許請求の範囲】

【請求項1】下記式Iで示されるアミド誘導体。



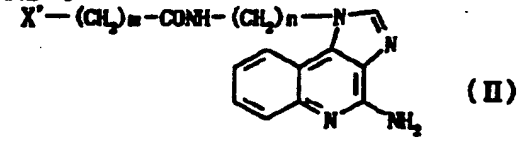
(I)

式I中、Xは水素原子またはハロゲン原子を表わし、mは1から9の整数を、nは2から12の整数を示す。

【請求項2】請求項1に記載のアミド誘導体を含有する医薬製剤。

【請求項3】下記式IIで示される合成中間体。

【化2】

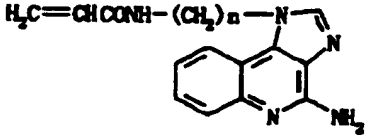


(II)

式II中、X'はハロゲン原子を表わし、mは1から9の整数を、nは2から12の整数を示す。

【請求項4】下記式II'で示される合成中間体。

【化3】

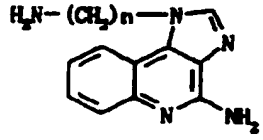


(II')

式II'中、nは2から12の整数を示す。

【請求項5】下記式IIIで示される合成中間体。

【化4】

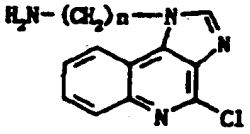


(III)

式III中、nは2から12の整数を示す。

【請求項6】下記式IVで示される合成中間体。

【化5】



(IV)

式IV中、nは2から12の整数を示す。

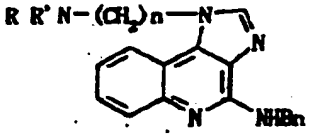
【請求項7】下記式Vで示される合成中間体。

【化6】

2

*【化1】

※

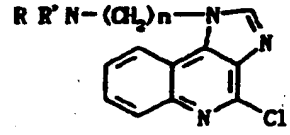


(V)

式V中、Rが水素のとき、R'は、炭素数1～8で分岐鎖を有してもよいアルカノイル基、炭素数1～8で分岐鎖を有してもよいハロアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェノキシアルカノイル基、炭素数1～8で分岐鎖を有してもよいアルコキシカルボニル基、炭素数1～8で分岐鎖を有してもよいハロアルコキシカルボニル基、あるいは炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルコキシカルボニル基を示す。また、R、R'が一つになってハロゲン、ニトロあるいはメトキシ置換基を有してもよい芳香族環状イミドを形成する。nは2から12の整数を示す。

【請求項8】下記式VIで示される合成中間体。

【化7】



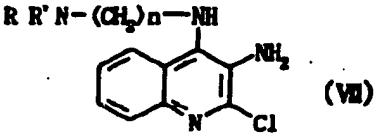
(VI)

式VI中、Rが水素のとき、R'は、炭素数1～8で分岐鎖を有してもよいアルカノイル基、炭素数1～8で分岐鎖を有してもよいハロアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェノキシアルカノイル基、炭素数1～8で分岐鎖を有してもよいアルコキシカルボニル基、炭素数1～8で分岐鎖を有してもよいハロアルコキシカルボニル基、あるいは炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルコキシカルボニル基を示す。また、R、R'が一つになってハロゲン、ニトロあるいはメト

キシ置換基を有してもよい芳香族環状イミドを形成する。nは2から12の整数を示す。

【請求項9】下記式VIIで示される合成中間体。

【化8】

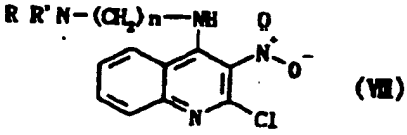


(VII)

式VII中、Rが水素のとき、R'は、炭素数1～8で分岐鎖を有してもよいアルカノイル基、炭素数1～8で分岐鎖を有してもよいハロアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェノキシアルカノイル基、炭素数1～8で分岐鎖を有してもよいアルコキシカルボニル基、炭素数1～8で分岐鎖を有してもよいハロアルコキシカルボニル基、あるいは炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルコキシカルボニル基を示す。また、R、R'が一つになってハロゲン、ニトロあるいはメトキシ置換基を有してもよい芳香族環状イミドを形成する。nは2から12の整数を示す。

【請求項10】下記式VIIIで示される合成中間体。

【化9】



(VIII)

式VIII中、Rが水素のとき、R'は、炭素数1～8で分岐鎖を有してもよいアルカノイル基、炭素数1～8で分岐鎖を有してもよいハロアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェノキシアルカノイル基、炭素数1～8で分岐鎖を有してもよいアルコキシカルボニル基、炭素数1～8で分岐鎖を有してもよいハロアルコキシカルボニル基、あるいは炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルコキシカルボニル基を示す。また、R、R'が一つになってハロゲン、ニトロあるいはメトキシ置換基を有してもよい芳香族環状イミドを形成する。nは2から12の整数を示す。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】本発明は、好酸球浸潤抑制作用および抗ヒスタミン作用を有し、アトピー性皮膚炎などの治療剤として有用な新規なアミド誘導体、およびそれを含有する医薬製剤、および合成中間体に関する。



【0002】

【従来の技術】アトピー性皮膚炎の治療には、従来より基本的にステロイド剤の外用と抗ヒスタミン剤あるいは抗アレルギー剤の内服が行われており、その他、減感作療法、アレルゲン（ダニ・食物）除去療法、PUVA（ソラレン－長波長紫外線照射）療法、細菌ワクチン療法などが試みられている。しかし、いずれも決め手となるものではなく、特にステロイド外用剤は、切れ味は良いが長期連投による皮膚の萎縮・毛細血管拡張・潮紅・紫斑・易感染性などの副作用が問題となっている。最近、アトピー性皮膚炎治療の方向はステロイドからサイトカイン療法に向かいつつある（中川秀巳.臨床免疫，27［supple 16］597－602，1995，小林祥子ら，臨床免疫，27［supple 16］603－609，1995）。アトピー性皮膚炎患者においては、Th1ヘルパー細胞とTh2ヘルパー細胞のバランスの不均衡すなわちTh2細胞優位の状態にあり、Th2細胞からのインターロイキン－4やインターロイキン－5などのサイトカインの産生増大の結果、好酸球等の炎症細胞の分化・増殖・浸潤を増強し炎症が惹起されるという説が有力となっている。従って、Th2細胞優位を抑制するインターフェロンや免疫抑制剤などが試みられているが、まだ、効果や副作用の点で満足できる結果が得られていない。

【0003】一般に、感作されたヒトの皮膚に抗原を投与すると投与直後と4～8時間後に最大となり24～48時間持続する皮膚反応が生じる。前者を即時型反応、後者を遅発型アレルギー反応と呼ぶ。特に遅発型反応は喘息を含むアレルギー疾患の病態と密接な関係があると指摘されている。遅発型反応のメカニズムは永らく不明であったが、今日ではIgE－肥満細胞が関与するI型アレルギー反応における時間的に遅れた相、すなわちlate phase reaction of the type I allergyであり、Th2ヘルパー細胞・好酸球が深く関わっていると考えられるようになった（黒沢元博，臨床免疫，27（5），564－574，1995）。このように、アトピー性皮膚炎は即時型と遅発型の両アレルギー反応が関与する疾患であり、遅発型反応の発症メカニズムも単一ではないと考えられるため、単に肥満細胞からのケミカルメディエーター遊離阻害剤や抗抗剤、あるいは炎症細胞浸潤抑制剤の単独使用では効果が不十分である。それゆえ、アトピー性皮膚炎の治療には肥満細胞から遊離するケミカルメディエーターのうち特に重要なヒスタミン（ヒスタミンは即時型だけでなく一部遅発型にも関与）と遅発型反応に関与することが知られている好酸球浸潤の両方を抑制する必要があるがそのような化合物は提示されていない。

【0004】また、本発明の化合物と類似した化合物が

幾つか公知となっている。例えば、1－置換－1H－イミダゾ［4，5－c］キノリン－4－アミン類としては、抗ウイルス剤である1－イソブチル－1H－イミダゾ［4，5－c］キノリン－4－アミン（イミキモド）を始めとしていくつか知られている（欧州特許第145340号、米国特許第4689338号、米国特許第4698348号、米国特許第4929624号、欧州特許第385630号、米国特許第5346905号等）。しかしながら、それらには抗ヒスタミン作用及び好酸球浸潤抑制作用は開示されていない。また、4－（ジフェニルメトキシ）－1－ピペリジンアルカン酸類は特開平3－264562号に開示されているが、好酸球浸潤抑制作用は記載されていない。

【0005】



＊【発明が解決しようとする課題】従って本発明は、十分な抗ヒスタミン作用および好酸球浸潤抑制作用を併せ持ち、アトピー性皮膚炎における主としてヒスタミン関与による即時型アレルギー反応と好酸球及びヒスタミン関与の遅発型アレルギー反応の両方の反応を抑える新規な化合物およびそれを含有する医薬製剤を提供することにある。

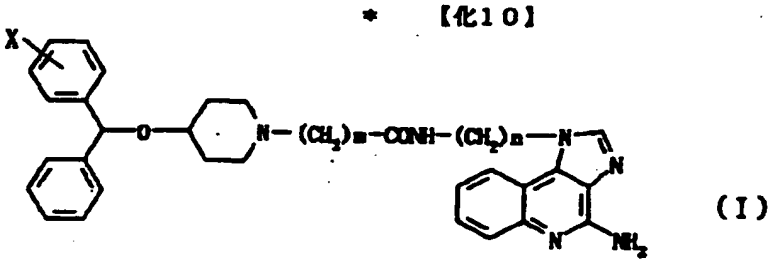
【0006】

【課題を解決するための手段】上記の課題を解決する本発明は以下の通りである。

（1）下記式Iで示されるアミド誘導体、およびその医薬的に許容しうる酸付加塩である。

【0007】

＊【化10】



(I)

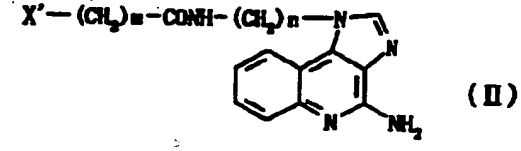
【0008】式I中、Xは水素原子またはハロゲン原子を表わし、mは1から9の整数を、nは2から12の整数を示す。

【0009】（2）上記（1）に記載のアミド誘導体を含有する医薬製剤である。

【0010】（3）下記式IIで示される式Iのアミド誘導体を合成するための合成中間体である。

【0011】

【化11】



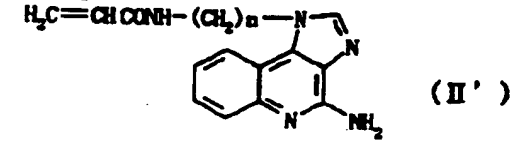
(II)

【0012】式II中、X'はハロゲン原子を表わし、mは1から9の整数を、nは2から12の整数を示す。

【0013】（4）下記式II'で示される式Iのアミド誘導体を合成するための合成中間体である。

【0014】

【化12】



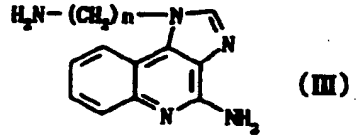
(II')

【0015】式II'中、nは2から12の整数を示す。

【0016】（5）下記式IIIで示される式Iのアミド誘導体を合成するための合成中間体である。

※【0017】

【化13】



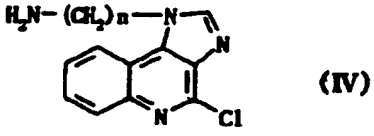
(III)

【0018】式III中、nは2から12の整数を示す。

【0019】（6）下記式IVで示される式Iのアミド誘導体を合成するための合成中間体である。

【0020】

【化14】



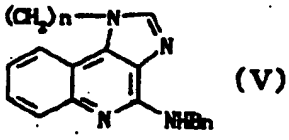
(IV)

【0021】式IV中、nは2から12の整数を示す。

【0022】（7）下記式Vで示される式Iのアミド誘導体を合成するための合成中間体である。

【0023】

【化15】



(V)

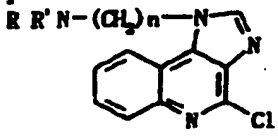
【0024】式V中、Rが水素のとき、R'は、炭素数1

～8で分岐鎖を有してもよいアルカノイル基、炭素数1～8で分岐鎖を有してもよいハロアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェノキシアルカノイル基、炭素数1～8で分岐鎖を有してもよいアルコキシカルボニル基、炭素数1～8で分岐鎖を有してもよいハロアルコキシカルボニル基、あるいは炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルコキシカルボニル基を示す。また、R、R'が一つになってハロゲン、ニトロあるいはメトキシ置換基を有してもよい芳香族環状イミドを形成する。nは2から12の整数を示す。

【0025】（8）下記式VIで示される式Iのアミド誘導体を合成するための合成中間体である。

【0026】

【化16】



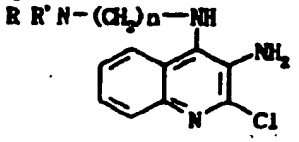
(VI)

【0027】式VI中、Rが水素のとき、R'は、炭素数1～8で分岐鎖を有してもよいアルカノイル基、炭素数1～8で分岐鎖を有してもよいハロアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェノキシアルカノイル基、炭素数1～8で分岐鎖を有してもよいアルコキシカルボニル基、炭素数1～8で分岐鎖を有してもよいハロアルコキシカルボニル基、あるいは炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルコキシカルボニル基を示す。また、R、R'が一つになってハロゲン、ニトロあるいはメトキシ置換基を有してもよい芳香族環状イミドを形成する。nは2から12の整数を示す。

【0028】（9）下記式VIIで示される式Iのアミド誘導体を合成するための合成中間体である。

【0029】

【化17】



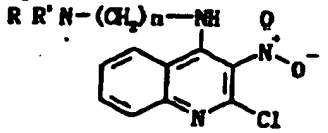
(VII)

【0030】式VII中、Rが水素のとき、R'は、炭素数1～8で分岐鎖を有してもよいアルカノイル基、炭素数1～8で分岐鎖を有してもよいハロアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェノキシアルカノイル基、炭素数1～8で分岐鎖を有してもよいアルコキシカルボニル基、炭素数1～8で分岐鎖を有してもよいハロアルコキシカルボニル基、あるいは炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルコキシカルボニル基を示す。また、R、R'が一つになってハロゲン、ニトロあるいはメトキシ置換基を有してもよい芳香族環状イミドを形成する。nは2から12の整数を示す。

【0031】（10）下記式VIIIで示される式Iのアミド誘導体を合成するための合成中間体である。

【0032】

【化18】



(VIII)

【0033】式VIII中、Rが水素のとき、R'は、炭素数1～8で分岐鎖を有してもよいアルカノイル基、炭素数1～8で分岐鎖を有してもよいハロアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルカノイル基、炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェノキシアルカノイル基、炭素数1～8で分岐鎖を有してもよいアルコキシカルボニル基、炭素数1～8で分岐鎖を有してもよいハロアルコキシカルボニル基、あるいは炭素数1～12でベンゼン環上ハロゲン、ニトロあるいはメトキシ置換基を有してもよいフェニルアルコキシカルボニル基を示す。また、R、R'が一つになってハロゲン、ニトロあるいはメトキシ置換基を有してもよい芳香族環状イミドを形成する。nは2から12の整数を示す。

【0034】式V、式VI、式VIIにおけるR、R'はアミノ基の保護基であり、好適には、アセチル、プロピオニル、ピバロイル、ベンゾイル、メトキシカルボニル、エトキシカルボニル、iso-ブトキシカルボニル、tert-ブトキシカルボニル、ベンジルオキシカルボニル、フタルイミドなどが挙げられる。

【0035】式Iの化合物の医薬的に許容しうる酸付加塩としては、塩酸、臭化水素酸、硫酸、硝酸、リン酸、酢酸、乳酸、マレイン酸、フマル酸、クエン酸、リンゴ酸、酒石酸、シュウ酸、メタンスルホン酸、p-トルエンスルホン酸などの塩が挙げられる。これらは常法により調製される。

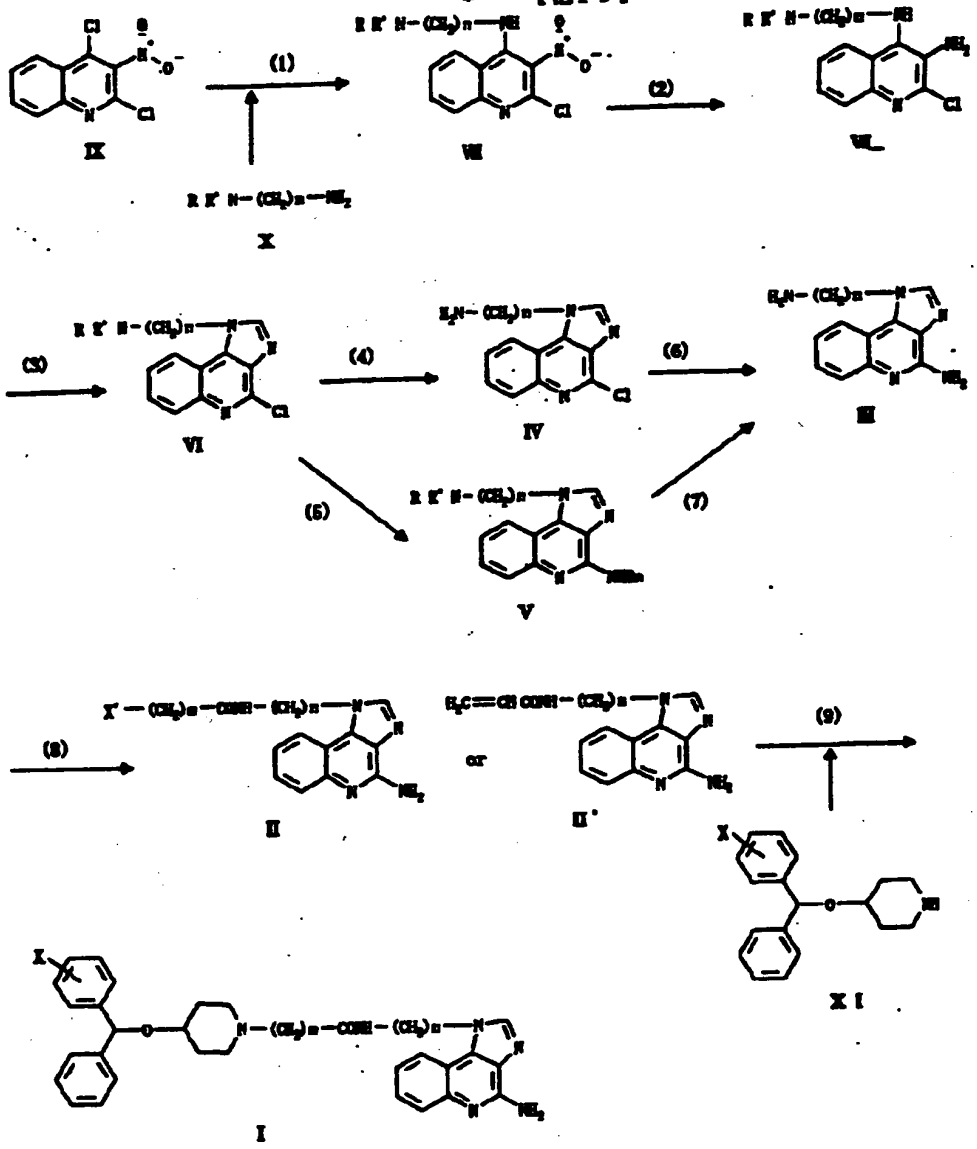
【0036】

【発明の実施の形態】本発明の式Iで示される新規なア

ミド誘導体は、例えば以下のようにして製造することができる。

＊【0037】

＊【化19】



【0038】工程（1）において、出発物質である式IXの2,4-ジクロロ-3-ニトロキノリンは公知物質であり、ガブリエルの方法（Chem.Ber.,1918,51,1500）等によって合成することができる。また、式Xのアルキレンジアミンのモノアミノ保護体も公知の方法（Synth.Commun.,1990,20,2559、J.Med.Chem.,1988,31,898、J.Org.Chem.,1981,46,2455、J.Amer.Chem.Soc.,1941,63,852等）によって合成することができる。式IXと式Xの化合物の反応は、適当な溶媒（好ましくはトリエチルアミンやピリジンのような塩基性溶媒）中で加熱することによって行なわれ、式VIIIの化合物を得ることができる。

＊【0039】工程（2）において、ニトロ基の還元は適当な溶媒（好ましくはアルコール）中で、鉄粉-塩酸あるいは塩化すず[II]によって0℃から還流温度で行うことができる。また、パラジウムや白金触媒存在下水素による接触還元によっても式VIIの化合物を得ることができる。

【0040】工程（3）において、式VIIの化合物をトリアルキルオルトホルメートと加熱するか、ギ酸金属塩存在下ギ酸中で加熱することによって、式VIの化合物を得ることができる。

【0041】工程（4）において、式VIの化合物のアミ

ノ保護基の脱保護反応は、保護基の種類に応じて適当な反応条件を選択することができる。たとえば、保護基がtert-ブトキシカルボニル（Boc）の場合は適当な溶媒中トリフルオロ酢酸で、ベンジルオキシカルボニル（Z）の場合は臭化水素-酢酸を選択することによって式IVの化合物を得ることができる。

【0042】工程（5）において、適当な溶媒中ベンジルアミンと加熱するか、無溶媒で過剰のベンジルアミンと加熱することによって式Vの化合物を得ることができる。

【0043】工程（6）において、オートクレーブ（耐圧鋼製ボンベ）中で、アルコール溶媒中のアンモニアあるいは濃アンモニア水と加熱して反応させることによって、式IIIの化合物を得ることができる。

【0044】工程（7）において、炭素担体上の水酸化パラジウムとともにカルボン酸（好ましくは、ギ酸）中で加熱することによって式IIIの化合物を得ることができる。

【0045】工程（8）において、式IIIの化合物をハロアルカン酸とともに適当な溶媒（たとえば、N,N-ジメチルホルムアミド）中、適当な縮合剤・縮合方法（たとえば、カルボジイミド、混合酸無水物法、酸クロライド法など）で縮合させることによって式IIの化合物に導くことができる。また、ハロアルカン酸の代わりに、適当な脱離基（たとえば、メタンスルホニルオキシ、p-トルエンスルホニルオキシなど）で置換されたアルカン酸を用いてもよい。

【0046】工程（9）において、式XIの化合物は公知物であり、式IIあるいはII'の化合物とともに適当な溶媒（ベンゼン、トルエン、キシレン、N,N-ジメチルホルムアミド、メタノール、エタノール、n-プロパノール、イソプロパノールなど）中加熱することによって式Iの化合物を得ることができる。またこの時、適当な塩基（たとえば、炭酸水素ナトリウム、炭酸カリウム、トリエチルアミンなど）を用いてもよい。

【0047】本発明の式Iで示されるアミド誘導体及びその医薬的に許容される酸付加塩は、アトピー性皮膚炎治療剤として経口及び非経口に哺乳動物に投与することができる。経口投与に用いる薬剤組成物の剤形は、錠剤、カプセル剤、散剤、細粒剤、顆粒剤、懸濁剤、乳剤、液剤、シロップなどが挙げられる。非経口投与に用いる剤形は、注射剤、坐剤、吸入剤、点眼剤、点鼻剤、軟膏、クリーム、ローション、貼付剤などが挙げられる。いずれの剤形においても、調製の際に適当な医薬・製剤的に許容しうる添加物を用いることができる。添加物としては、賦形剤、結合剤、滑沢剤、崩壊剤、希釈剤、風味剤、着色剤、溶解剤、懸濁剤、乳化剤、保存剤、緩衝剤、等張化剤、軟膏基剤、オイル、溶解補助剤、吸収促進剤、接着剤、噴霧剤などが挙げられる。

【0048】式Iの化合物及びその酸付加塩は、好ましくは軟膏、ローション、クリームなどの経皮投与のための製剤の形をとる。

【0049】式Iの化合物及びその酸付加塩は、好酸球浸潤抑制作用及び抗ヒスタミン作用を示すことから、それらの作用が効果を及ぼす他の疾患、たとえばアレルギー性鼻炎、じん麻疹、喘息などに有用であることが示唆される。

【0050】

【実施例】次に、本発明を実施例によってさらに詳細に説明する。なお、実施例にて合成した化合物の分光学的データは、IRスペクトルは日本分光IR-810、$^1$H-NMRスペクトルは Varian Unity 400 NMR Apparatus により測定した。

【0051】（実施例1）

4-[3-(ベンジルオキシカルボニルアミノ)プロピルアミノ]-2-クロロ-3-ニトロキノリンの合成

2,4-ジクロロ-3-ニトロキノリン0.19g（0.768mmol）及びN-(ベンジルオキシカルボニル)-1,3-プロパンジアミン0.16g（0.768mmol）をトリエチルアミン5ml中、70℃に加熱して1時間撹拌した。トリエチルアミンを減圧下留去した後、塩化メチレンに溶解し、水洗、乾燥（$MgSO_4$）後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィーに付し、n-ヘキサン-酢酸エチル（2：1v/v）溶出画分により、4-[3-(ベンジルオキシカルボニルアミノ)プロピルアミノ]-2-クロロ-3-ニトロキノリン0.27g（0.651mmol）を黄色粉末として得た。このものの分光学的データは以下の通りである。

【0052】$^1$H-NMR（$CDCl_3$）$\delta$（ppm）：1.79（2H,m），3.35（4H,m），5.02（1H,br），5.18（2H,s），7.15（1H,br），7.37（5H,m），7.57（1H,t,J=8.0Hz），7.73（1H,t,J=7.8Hz），7.90（1H,d,J=8.4Hz），8.21（1H,d,J=8.0Hz）

【0053】（実施例2）

3-アミノ-4-[3-(ベンジルオキシカルボニルアミノ)プロピルアミノ]-2-クロロキノリンの合成

4-[3-(ベンジルオキシカルボニルアミノ)プロピルアミノ]-2-クロロ-3-ニトロキノリン0.27g（0.651mmol）をメタノール10mlに溶解し、濃塩酸1ml及び鉄粉0.22g（0.390mmol）を加え室温で2時間撹拌した。反応液を飽和炭酸水素ナトリウム水溶液にあけ、酢酸エチルで抽出し、食塩水で洗浄、乾燥（$Na_2SO_4$）後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール（300：1v/v）溶出画分により、3-アミノ-4-[3-(ベンジルオキシカルボニルアミノ)プロピルアミノ]-2-クロロキノリン0.12g

(0.312mmol)を微黄色粉末として得た。このものの分光学的データは以下の通りである。

【0054】$^1$H-NMR(CDCl$_3$) δ(ppm):1.76(2H,m),3.30(2H,m),3.42(2H,q,J=6.3Hz),4.21(2H,bs),4.44(1H,br),4.92(1H,br),5.16(2H,s),7.30-7.39(5H,m),7.46(2H,m),7.89(2H,m)

【0055】(実施例3)

1-[3-(ベンジルオキシカルボニルアミノ)プロピル]-4-クロロ-1H-イミダゾ[4,5-c]キノリンの合成

3-アミノ-4-[3-(ベンジルオキシカルボニルアミノ)プロピルアミノ]-2-クロロキノリン0.12g(0.312mmol)にトリエチルオルトホルメート0.52ml(3.12mmol)を加え、100℃に加熱して3.5時間撹拌した。反応液を減圧下濃縮して、1-[3-(ベンジルオキシカルボニルアミノ)プロピル]-4-クロロ-1H-イミダゾ[4,5-c]キノリン0.12g(0.304mmol)を淡黄色固体として得た。このものの分光学的データは以下の通りである。

【0056】$^1$H-NMR(CDCl$_3$) δ(ppm):2.24(2H,m),3.36(2H,q,J=6.4Hz),4.67(2H,t,J=7.0Hz),4.95(1H,br),5.14(2H,s),7.31-7.39(5H,m),7.62(1H,t,J=7.8Hz),7.71(1H,t,J=7.8Hz),8.09(1H,s),8.13(1H,d,J=8.4Hz),8.21(1H,d,J=8.4Hz)

【0057】(実施例4)

1-(3-アミノプロピル)-4-クロロ-1H-イミダゾ[4,5-c]キノリン・酢酸塩の合成

1-[3-(ベンジルオキシカルボニルアミノ)プロピル]-4-クロロ-1H-イミダゾ[4,5-c]キノリン0.12g(0.304mmol)に臭化水素-酢酸[33%] 3mlを加え、室温で1.5時間撹拌した。反応液を減圧下濃縮し、残渣に1N-水酸化ナトリウム水溶液及び食塩水を加えクロロホルムで5回抽出した。乾燥($Na_2SO_4$)後溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール-32%酢酸(12:6:1v/v)溶出画分により、1-(3-アミノプロピル)-4-クロロ-1H-イミダゾ[4,5-c]キノリン・酢酸塩60mg(0.187mmol)を淡黄色固体として得た。このものの分光学的データは以下の通りである。

【0058】$^1$H-NMR($CD_3OD$) δ(ppm):1.94(3H,s),2.39(2H,m),3.12(2H,t,J=7.8Hz),4.82(2H,t,J=7.2Hz),7.70(2H,m),7.97(1H,d,J=8.0Hz),8.27(1H,d,J=8.0Hz),8.41(1H,s)

【0059】(実施例5)

1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

1-(3-アミノプロピル)-4-クロロ-1H-イミダゾ[4,5-c]キノリン・酢酸塩60mg(0.187mmol)を耐圧鋼製反応管に入れ、メタノール10ml及び冷却下液体アンモニア5mlを加え、150℃に加熱して1晩撹拌した。反応液を減圧下濃縮し、残渣を少量の水に溶解し1N-水酸化ナトリウム水溶液0.5mlを加えた。析出物を沪取しエタノールから再結晶して、1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミン11mg(0.0455mmol)を淡黄色綿状結晶(mp:243~245℃(分解))として得た。このものの分光学的データは以下の通りである。

【0060】IR(KBr) cm$^{-1}$:3320,3170,1650

$^1$H-NMR(DMSO-d$_6$) δ(ppm):1.93(2H,m),2.57(2H,t,J=6.6Hz),4.64(2H,t,J=7.0Hz),6.55(2H,s),7.26(1H,t,J=7.2Hz),7.44(1H,t,J=7.4Hz),7.62(1H,d,J=8.0Hz),8.12(1H,d,J=8.0Hz),8.19(1H,s)

【0061】(実施例6)

4-[3-(tert-ブトキシカルボニルアミノ)プロピルアミノ]-2-クロロ-3-ニトロキノリンの合成

2,4-ジクロロ-3-ニトロキノリン0.59g(2.41mmol)及びN-(tert-ブトキシカルボニル)-1,3-プロパンジアミン0.42g(2.41mmol)をトリエチルアミン10ml中、70℃に加熱して1.5時間撹拌した。減圧下トリエチルアミンを留去し、残渣を塩化メチレンに溶解し、水洗、乾燥($Na_2SO_4$)後減圧下濃縮した。残渣をメタノールでトリチュレートして沪取し、4-[3-(tert-ブトキシカルボニルアミノ)プロピルアミノ]-2-クロロ-3-ニトロキノリン0.61g(1.60mmol)を黄色結晶(mp:159~161℃)として得た。このものの分光学的データは以下の通りである。

【0062】IR(KBr) cm$^{-1}$:3310,1680,1580

$^1$H-NMR(CDCl$_3$) δ(ppm):1.50(9H,s),1.77(2H,m),3.27(2H,q,J=6.1Hz),3.36(2H,q,J=6.0Hz),4.82(1H,br),7.37(1H,br),7.55(1H,t,J=7.8Hz),7.72(1H,t,J=7.7Hz),7.89(1H,d,J=8.2Hz),8.27(1H,d,J=8.4Hz)

【0063】(実施例7)

3-アミノ-4-[3-(tert-ブトキシカルボニルア

ミノ）プロピルアミノ]－2－クロロキノリンの合成
4－[3－(tert－ブトキシカルボニルアミノ)プロピルアミノ]－2－クロロ－3－ニトロキノリン0.27g(0.70mmol)をエタノール7mlに溶解し、塩化すず[II]・2水和物0.55g(2.45mmol)を加え1時間加熱還流した。冷却後反応液を2N－アンモニア水にあけ、クロロホルムで2回抽出し、洗浄(食塩水)、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーに付し、n－ヘキサン－酢酸エチル(1：1v/v)溶出画分により、3－アミノ－4－[3－(tert－ブトキシカルボニルアミノ)プロピルアミノ]－2－クロロキノリン0.15g(0.428mmol)を淡黄色結晶として得た。このものの分光学的データは以下の通りである。

【0064】$^1$H－NMR(CDCl$_3$) $\delta$(ppm)：1.49(9H,s)，1.73(2H,m)，3.29(2H,t,J=6.2Hz)，3.35(2H,q,J=6.0Hz)，4.28(2H,bs)，4.60(1H,br)，4.75(1H,br)，7.44(2H,m)，7.87(1H,d,J=7.6Hz)，7.94(1H,d,J=7.6Hz)

【0065】(実施例8)

1－[3－(tert－ブトキシカルボニルアミノ)プロピル]－4－クロロ－1H－イミダゾ[4,5－c]キノリンの合成

3－アミノ－4－[3－(tert－ブトキシカルボニルアミノ)プロピルアミノ]－2－クロロキノリン0.15g(0.428mmol)にトリエチルオルトホルメート0.36ml(2.14mmol)を加えて、100℃で2時間さらに80℃で1晩撹拌した。反応混合物を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム－メタノール(150：1～100：1v/v)溶出画分により、1－[3－(tert－ブトキシカルボニルアミノ)プロピル]－4－クロロ－1H－イミダゾ[4,5－c]キノリン0.14g(0.388mmol)を白色粉末(mp：155～156℃)として得た。このものの分光学的データは以下の通りである。

【0066】IR(KBr) cm$^{-1}$：3380，1680，1520

$^1$H－NMR(CDCl$_3$) $\delta$(ppm)：1.47(9H,s)，2.22(2H,m)，3.30(2H,q,J=6.4Hz)，4.68(2H,t,J=7.2Hz)，4.7(1H,br)，7.66(1H,t,J=7.6Hz)，7.72(1H,t,J=7.6Hz)，8.09(1H,s)，8.16(1H,d,J=8.4Hz)，8.21(1H,d,J=8.4Hz)

【0067】(実施例9)

1－(3－アミノプロピル)－4－クロロ－1H－イミダゾ[4,5－c]キノリンの合成

1－[3－(tert－ブトキシカルボニルアミノ)プロピル]－4－クロロ－1H－イミダゾ[4,5－c]キノリン50mg(0.139mmol)を塩化メチレン3mlに溶解し、トリフルオロ酢酸0.11ml(1.39mmol)を加え室温で1日撹拌した。反応液を減圧下濃縮し、残渣に1N－水酸化ナトリウム水溶液1ml及び食塩水を加え、クロロホルムで5回抽出し、乾燥($Na_2SO_4$)後減圧下濃縮した。残渣をジエチルエーテル(塩化メチレンを少量含む)でトリチュレートして析出物を戸取し、1－(3－アミノプロピル)－4－クロロ－1H－イミダゾ[4,5－c]キノリン14mg(0.0536mmol)を白色粉末として得た。このものの分光学的データは以下の通りである。

【0068】IR(KBr) cm$^{-1}$：3400，1590，1510

$^1$H－NMR(CDCl$_3$+CD$_3$OD) $\delta$(ppm)：2.06(2H,m)，2.72(2H,t,J=6.8Hz)，2.98(2H,br)，4.64(2H,t,J=7.0Hz)，7.57(1H,t,J=7.6Hz)，7.61(1H,t,J=7.6Hz)，8.03(1Hs)，8.05(1H,d,J=8.0Hz)，8.11(1H,d,J=8.0Hz)

【0069】(実施例10)

1－(3－アミノプロピル)－1H－イミダゾ[4,5－c]キノリン－4－アミンの合成(その2)

1－(3－アミノプロピル)－4－クロロ－1H－イミダゾ[4,5－c]キノリン14mg(0.0536mmol)を耐圧鋼製反応管に入れ、メタノール5ml及び冷却下液体アンモニア3mlを加え、150℃に加熱して1晩撹拌した。反応液を減圧下濃縮し、残渣に1N－水酸化ナトリウム水溶液0.3mlを加え析出物を戸取して、1－(3－アミノプロピル)－1H－イミダゾ[4,5－c]キノリン－4－アミン8mg(0.0331mmol)を得た。このものの物性値は、実施例5の化合物と一致した。

【0070】(実施例11)

4－ベンジルアミノ－1－[3－(tert－ブトキシカルボニルアミノ)プロピル]－1H－イミダゾ[4,5－c]キノリンの合成

1－[3－(tert－ブトキシカルボニルアミノ)プロピル]－4－クロロ－1H－イミダゾ[4,5－c]キノリン30mg(0.0831mmol)にベンジルアミン1mlを加え、150℃に加熱して3時間撹拌した。減圧下過剰のベンジルアミンを留去し、1N－塩酸と食塩水を加え塩化メチレンで2回抽出した。有機相を飽和炭酸水素ナトリウム水溶液で洗浄し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム－メタノール(150：1v/v)溶出画分により、4－ベンジルアミノ－1－[3－(tert－ブトキシカルボニルアミノ)プロピル]－1H－イミダゾ[4,5－c]キノリン35mg

(0.0811mmol)を白色粉末(mp:171～172.5℃)として得た。このものの分光学的データは以下の通りである。

【0071】IR(KBr)cm⁻¹:3330, 1700, 1590, 1540

¹H-NMR(CDCl₃)δ(ppm):1.46(9H,s), 2.18(2H,m), 3.25(2H,m), 4.57(2H,t,J=7.0Hz), 4.64(1H,br), 4.95(2H, d, J=5.2Hz), 6.05(1H,br), 7.26-7.36(4H,m), 7.47(2H,d,J=7.6Hz), 7.51(1H,t,J=7.6Hz), 7.82(1H,s), 7.92(2H,t,J=8.0Hz)

【0072】(実施例12)

1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成(その3)

4-ベンジルアミノ-1-[3-(tert-ブトキシカルボニルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン30mg(0.0695mmol)をギ酸3mlに溶解し、水酸化パラジウム-炭素[20%]0.1gを加え1日加熱還流した。反応液を沪過し減圧下溶媒を留去した後、残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール-32%酢酸(6:3:1v/v)溶出画分より目的物の酢酸塩を得、アルカリ処理で結晶を沪取し、1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミン7mg(0.0290mmol)を微褐色粉末として得た。このものの物性値は、実施例5の化合物と一致した。

【0073】(実施例13)

4-[4-(tert-ブトキシカルボニルアミノ)ブチルアミノ]-2-クロロ-3-ニトロキノリンの合成

2,4-ジクロロ-3-ニトロキノリン0.72g(2.97mmol)及びN-(tert-ブトキシカルボニル)-1,4-ジアミノブタン0.56g(2.97mmol)をトリエチルアミン12ml中、70℃に加熱して1.5時間撹拌した。減圧下濃縮し、残渣を塩化メチレンに溶解し、水洗、乾燥(MgSO₄)後、減圧下溶媒を留去した。残渣をn-ヘキサン-ジエチルエーテル(1:1v/v)でトリチュレートして沪取し、4-[4-(tert-ブトキシカルボニルアミノ)ブチルアミノ]-2-クロロ-3-ニトロキノリン0.97g(2.46mmol)を黄色粉末(mp:125～126.5℃)として得た。このものの分光学的データは以下の通りである。

【0074】IR(KBr)cm⁻¹:3340, 3280, 1680, 1540, 1520

¹H-NMR(CDCl₃)δ(ppm):1.46(9H,s), 1.63(2H,m), 1.78(2H,m), 3.19(2H,q,J=6.4Hz), 3.47(2H,q,J=6.1Hz), 4.68(1H,br), 6.41(1H,br), 7.52(1H,t,J=7.7Hz), 7.74(1H,t,J=7.8Hz), 7.91(1H,d,J=8.4Hz), 8.11(1H,d,J=8.4Hz)

【0075】(実施例14)

3-アミノ-4-[4-(tert-ブトキシカルボニルアミノ)ブチルアミノ]-2-クロロキノリンの合成

4-[4-(tert-ブトキシカルボニルアミノ)ブチルアミノ]-2-クロロ-3-ニトロキノリン0.5g(1.27mmol)をエタノール13mlに溶解し、塩化すず[II]・2水和物1.0g(4.43mmol)を加え1時間加熱還流した。反応液を2N-アンモニア水にあけ、クロロホルムで2回抽出し、洗浄(食塩水)、乾燥(Na₂SO₄)後、減圧下溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーに付し、n-ヘキサン-酢酸エチル(2:1v/v)溶出画分により目的物を集め、溶媒留去後ジエチルエーテルでトリチュレートして、3-アミノ-4-[4-(tert-ブトキシカルボニルアミノ)ブチルアミノ]-2-クロロキノリン0.12g(0.329mmol)を橙色結晶として得た。このものの分光学的データは以下の通りである。

【0076】IR(KBr)cm⁻¹:3270, 1680, 1540, 760

¹H-NMR(CDCl₃)δ(ppm):1.44(9H,s), 1.64(4H,m), 3.17(2H,q,J=6.0Hz), 3.27(2H,t,J=6.6Hz), 3.89(1H,br), 4.15(2H,bs), 4.59(1H,br), 7.47(2H,m), 7.77(1H,d,J=7.6Hz), 7.89(1H,d,J=7.2Hz)

【0077】(実施例15)

1-[4-(tert-ブトキシカルボニルアミノ)ブチル]-4-クロロ-1H-イミダゾ[4,5-c]キノリンの合成

3-アミノ-4-[4-(tert-ブトキシカルボニルアミノ)ブチルアミノ]-2-クロロキノリン0.14g(0.384mmol)にトリエチルオルトホルメート0.32ml(1.92mmol)を加え、100℃に加熱して1晩撹拌した。反応混合物を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール(150:1～100:1v/v)溶出画分により、1-[4-(tert-ブトキシカルボニルアミノ)ブチル]-4-クロロ-1H-イミダゾ[4,5-c]キノリン0.12g(0.321mmol)を淡橙色粉末(mp:148～150℃)として得た。このものの分光学的データは以下の通りである。

【0078】IR(KBr)cm⁻¹:1695, 1510

¹H-NMR(CDCl₃)δ(ppm):1.42(9H,s), 1.62(2H,m), 2.06(2H,m), 3.21(2H,q,J=6.4Hz), 4.58(1H,br), 4.65(2H,t,J=7.4Hz), 7.66(1H,t,J=7.2Hz), 7.72(1H,t,J=7.6H

z)，8.02(1H,s)，8.13(1H,d,J=8.4Hz)，8.21(1H,d,J=8.2Hz)

【0079】(実施例16)

1-(4-アミノブチル)-4-クロロ-1H-イミダゾ[4,5-c]キノリンの合成

1-[4-(tert-ブトキシカルボニルアミノ)ブチル]-4-クロロ-1H-イミダゾ[4,5-c]キノリン0.10g(0.267mmol)を塩化メチレン6mlに溶解し、トリフルオロ酢酸0.21ml(2.67mmol)を加え室温で1晩撹拌した。反応液を減圧下濃縮し、残渣に1N-水酸化ナトリウム水溶液2ml及び食塩水を加えてクロロホルムで5回抽出し、乾燥($Na_2SO_4$)後減圧下濃縮した。残渣をジエチルエーテル(塩化メチレンを少量含む)でトリチュレートして析出物を沪取し、1-(4-アミノブチル)-4-クロロ-1H-イミダゾ[4,5-c]キノリン45mg(0.164mmol)を淡褐色粉末として得た。このものの分光学的データは以下の通りである。

【0080】IR(KBr)$cm^{-1}$:3400,2950,1670,1520,1360

$^1$H-NMR($CDCl_3$)$\delta$(ppm):1.51(2H,m)，1.96(2H,m)，2.66(2H,t,J=7.2Hz)，3.03(2H,bs)，4.53(2H,t,J=7.4Hz)，7.56(1H,t,J=7.4Hz)，7.60(1H,t,J=7.5Hz)，7.97(1H,s)，8.02(1H,d,J=6.4Hz)，8.04(1H,d,J=6.4Hz)

【0081】(実施例17)

1-(4-アミノブチル)-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

1-(4-アミノブチル)-4-クロロ-1H-イミダゾ[4,5-c]キノリン40mg(0.146mmol)を耐圧鋼製反応管に入れ、メタノール8ml及び冷却下液体アンモニア4mlを加え、150℃に加熱して1晩撹拌した。反応液を減圧下濃縮し、残渣を少量の水に溶解し、1N-水酸化ナトリウム水溶液0.5mlを加えた。析出物を沪取しエタノールから再結晶して、1-(4-アミノブチル)-1H-イミダゾ[4,5-c]キノリン-4-アミン14mg(0.0548mmol)を淡黄緑色結晶(mp:227～230.5℃(分解))として得た。このものの分光学的データは以下の通りである。

【0082】IR(KBr)$cm^{-1}$:3340,3180,1650,1530,1400

$^1$H-NMR(DMSO-$d_6$)$\delta$(ppm):1.30(2H,br)，1.39(2H,m)，1.89(2H,m)，2.55(2H,t,J=6.8Hz)，4.59(2H,t,J=7.0Hz)，6.56(2H,bs)，7.26(1H,t,J=7.4Hz)，7.44(1H,t,J=7.7Hz)，7.62(1H,d,J=8.0Hz)，8.05(1H,d,J=8.0Hz)，8.19(1H,s)

【0083】(実施例18)

4-ベンジルアミノ-1-[4-(tert-ブトキシカルボニルアミノ)ブチル]-1H-イミダゾ[4,5-c]キノリンの合成

1-[4-(tert-ブトキシカルボニルアミノ)ブチル]-4-クロロ-1H-イミダゾ[4,5-c]キノリン70mg(0.187mmol)にベンジルアミン2mlを加え、150℃に加熱して3時間撹拌した。減圧下過剰のベンジルアミンを留去し、1N-塩酸及び食塩水を加え塩化メチレンで2回抽出した。有機層を飽和炭酸水素ナトリウム水溶液で洗浄し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール(150:1v/v)溶出画分により、4-ベンジルアミノ-1-[4-(tert-ブトキシカルボニルアミノ)ブチル]-1H-イミダゾ[4,5-c]キノリン79mg(0.177mmol)を白色粉末(mp:151～153.5℃)として得た。このものの分光学的データは以下の通りである。

【0084】IR(KBr)$cm^{-1}$:3380,3310,2930,1680,1595,1540,1245,1160

$^1$H-NMR($CDCl_3$)$\delta$(ppm):1.42(9H,s)，1.58(2H,m)，2.02(2H,m)，3.18(2H,m)，4.55(2H,t,J=7.4Hz)，4.55(1H,br)，4.95(2H,d,J=5.6Hz)，6.03(1H,t,J=5.6Hz)，7.23-7.36(4H,m)，7.47(2H,d,J=7.6Hz)，7.51(1H,t,J=7.8Hz)，7.75(1H,s)，7.90(2H,d,J=8.0Hz)

【0085】(実施例19)

1-(4-アミノブチル)-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

4-ベンジルアミノ-1-[4-(tert-ブトキシカルボニルアミノ)ブチル]-1H-イミダゾ[4,5-c]キノリン67mg(0.150mmol)をギ酸5mlに溶解し、水酸化パラジウム-炭素[20%]0.15gを加え2日間加熱還流した。反応液を沪過し、減圧下溶媒を留去した後残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール-32%酢酸(6:3:1v/v)溶出画分より目的物の酢酸塩を得、アルカリ処理して固体を沪取し、1-(4-アミノブチル)-1H-イミダゾ[4,5-c]キノリン-4-アミン14mg(0.0548mmol)を微褐色粉末として得た。このものの物性値は、実施例17の化合物と一致した。

【0086】(実施例20)

1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンアセチル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

a) クロロ酢酸0.10g(1.1mmol)及び1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミン0.24g(1mmol)をN,N-ジメチルホルムアミド30mlに懸濁し、1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・塩酸塩(EDCI)0.29g(1.5mmol)を加えて室温で1晩撹拌した。反応液に水を加え、クロロホルムで1回、クロロホルム-メタノール(10:1v/v)で3回抽出した。有機層を食塩水で洗浄し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去して、1-[3-[(クロロアセチル)アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの粗生成物を得た。この化合物は不安定なため、精製せずに次の反応に用いた。

【0087】b) a)で得られた1-[3-[(クロロアセチル)アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの粗生成物をエタノール5mlに溶解し、4-(ジフェニルメトキシ)ピペリジン・塩酸塩0.14g(0.472mmol)及び炭酸水素ナトリウム48mg(0.566mmol)を加え、7時間加熱還流した。不溶物を沪過して除き、沪液を減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール(30:1~20:1v/v)溶出画分により、1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンアセチル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン20mg(0.0364mmol)を淡黄色非晶質として得た。このものの分光学的データは以下の通りである。

【0088】IR(KBr)$cm^{-1}$:3320, 1650, 1525, 1070, 700

$^1$H-NMR(CDCl$_3$)$\delta$(ppm):1.70(2H,m), 1.86(2H,m), 2.19(2H,m), 2.27(2H,t,J=10.4Hz), 2.74(2H,m), 2.98(2H,s), 3.39(2H,q,J=6.5Hz), 3.45(1H,m), 4.54(2H,t,J=7.0Hz), 5.49(1H,s), 5.60(2H,bs), 7.21-7.36(10H,m), 7.38(1H,t,J=7.2Hz), 7.51(1H,t,J=7.7Hz), 7.82(1H,d,J=8.2Hz), 7.89(1H,s), 7.90(1H,d,J=8.0Hz)

【0089】(実施例21)

<u>1-[3-(アクリルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成</u>

1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミン0.24g(1mmol)をN,N-ジメチルホルムアミド30mlに懸濁し、アクリル酸75μl(1.1mmol)及び1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・塩酸塩0.29g(1.5mmol)を加え室温で3.5時間撹拌した。反応液に水を加え、クロロホルムで1回、クロロホルム-メタノール(10:1v/v)で4回抽出した。有機層を食塩水で洗浄し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール(8:1v/v)溶出画分により目的物を集め、溶媒留去後少量のクロロホルムでトリチュレートして沪取し、1-[3-(アクリルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン0.14g(0.474mmol)を微黄色粉末(mp:173~175℃)として得た。このものの分光学的データは以下の通りである。

【0090】IR(KBr)$cm^{-1}$:3330, 3200, 1630, 1525

$^1$H-NMR(CDCl$_3$)$\delta$(ppm):2.25(2H,m), 3.47(2H,q,J=6.5Hz), 4.61(2H,t,J=7.0Hz), 5.47(2H,bs), 5.71(1H,br), 6.09(1H,dd,J=16.8, 10.4Hz), 6.32(1H,d,J=16.8Hz), 7.33(1H,t,J=7.6Hz), 7.53(1H,t,J=7.8Hz), 7.83(1H,d,J=8.4Hz), 7.92(1H,s), 7.93(1H,d,J=8.2Hz)

【0091】(実施例22)

<u>1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンプロパノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成</u>

1-[3-(アクリルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン0.12g(0.406mmol)をエタノール10mlに溶解し、4-(ジフェニルメトキシ)ピペリジン・塩酸塩0.13g(0.427mmol)及び炭酸水素ナトリウム38mg(0.447mmol)を加え、1晩加熱還流した。不溶物を沪過して除き、沪液を濃縮し、残渣をアルミナカラムクロマトグラフィーに付した。クロロホルム-メタノール(40:1v/v)溶出画分により目的物を集め、溶媒留去後エーテルでトリチュレートして沪取し、1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンプロパノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン75mg(0.133mmol)を微黄色粉末(mp:178~182℃)として得た。このものの分光学的データは以下の通りである。

【0092】IR(KBr)$cm^{-1}$:3330, 3200, 1640, 1530, 1080, 700

$^1$H-NMR(CDCl$_3$)$\delta$(ppm):1.61(2H,m), 1.84(2H,m), 2.13(2H,m), 2.20(2H,m), 2.38(2H,t,J=6.0Hz), 2.54(2H,t,J=6.0Hz), 2.74(2H,m), 5.48(1H,s), 7.21-7.54(11H,m), 7.51(1H,t,J=7.7Hz), 7.83(1H,d,J=8.4Hz), 7.91(1H,s), 7.94(1H,d,J=8.4Hz), 8.68(1H,br)

【0093】(実施例23)
1-[4-(アクリルアミノ)ブチル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成
1-(4-アミノブチル)-1H-イミダゾ[4,5-c]キノリン-4-アミン0.26g(1mmol)をN,N-ジメチルホルムアミド30mlに懸濁し、アクリル酸75μl(1.1mmol)及び1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・塩酸塩0.29g(1.5mmol)を加え室温で1晩撹拌した。反応液に水を加え、クロロホルムで1回さらにクロロホルム-メタノール(10:1v/v)で4回抽出した。有機層を食塩水で洗浄し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム-メタノール(10:1~8:1v/v)溶出画分により、1-[4-(アクリルアミノ)ブチル]-1H-イミダゾ[4,5-c]キノリン-4-アミン90mg(0.291mmol)を淡黄色粉末(mp:176~178℃)として得た。このものの分光学的データは以下の通りである。
【0094】IR(KBr)$cm^{-1}$:3320,3200,1640,1530
$^1$H-NMR($CDCl_3$)δ(ppm):1.65(2H,m),2.04(2H,m),3.40(2H,q,J=6.7Hz),4.58(2H,t,J=7.2Hz),5.50(2H,br),5.52(1H,br),5.65(1H,d,J=10.2Hz),6.03(1H,dd,J=16.8,10.4Hz),6.27(1H,d,J=17.0Hz),7.33(1H,t,J=7.6Hz),7.53(1H,t,J=7.7Hz),7.83(1H,s),7.83(1H,d,J=8.6Hz),7.93(1H,d,J=8.4Hz)
【0095】(実施例24)
1-[4-[[4-(ジフェニルメトキシ)-1-ピペリジンプロパノイル]アミノ]ブチル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成
1-[4-(アクリルアミノ)ブチル]-1H-イミダゾ[4,5-c]キノリン-4-アミン85mg(0.275mmol)をエタノール7mlに溶解し、4-(ジフェニルメトキシ)ピペリジン・塩酸塩88mg(0.288mmol)及び炭酸水素ナトリウム25mg(0.302mmol)を加え、1晩加熱還流した。不溶物を沪過して除き、沪液を濃縮し、残渣をアルミナカラムクロマトグラフィーに付した。クロロホルム-メタノール(50:1v/v)溶出画分により目的物を集め、溶媒留去後エーテルでトリチュレートして沪取し、1-[4-[[4-(ジフェニルメトキシ)-1-ピペリジンプロパノイル]アミノ]ブチル]-1H-イミダゾ[4,5-c]キノリン-4-アミン48mg(0.0832mmol)を白色粉末(mp:174~176℃)として得た。このものの分光学的データは以下の通りである。
【0096】IR(KBr)$cm^{-1}$:3370,3100,2950,1640,1530,1090,750,705
$^1$H-NMR($CDCl_3$)δ(ppm):1.48-1.63(4H,m),1.77(2H,m),2.01(4H,m),2.30(2H,t,J=6.0Hz),2.44(2H,t,J=6.0Hz),2.63(2H,m),3.28(2H,q,J=6.5Hz),3.37(1H,m),4.56(2H,t,J=7.2Hz),5.42(2H,bs),5.47(1H,s),7.21-7.35(11H,m),7.51(1H,t,J=7.7Hz),7.81(1H,s),7.82(1H,d,J=8.0Hz),7.92(1H,d,J=8.0Hz),8.58(1H,br)
【0097】(実施例25)
1-[3-[[4-[(4-クロロフェニル)フェニルメトキシ]-1-ピペリジンプロパノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成
1-[3-(アクリルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン50mg(0.169mmol)をエタノール5mlに溶解し、4-[(4-クロロフェニル)フェニルメトキシ]ピペリジン・塩酸塩60mg(0.178mmol)及び炭酸水素ナトリウム16mg(0.186mmol)を加えて1日加熱還流した。不溶物を沪過した後、溶媒を留去し、残渣をアルミナカラムクロマトグラフィーに付した。クロロホルム-メタノール(40:1v/v)溶出画分により目的物を集め、溶媒留去後エーテルでトリチュレートして沪取し、1-[3-[[4-[(4-クロロフェニル)フェニルメトキシ]-1-ピペリジンプロパノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン40mg(0.0669mmol)を白色粉末(mp:170~172.5℃)として得た。このものの分光学的データは以下の通りである。
【0098】IR(KBr)$cm^{-1}$:3320,3200,2940,1640,1530,1080
$^1$H-NMR($CDCl_3$)δ(ppm):1.59(2H,m),1.81(2H,m),2.13(2H,m),2.20(2H,m),2.37(2H,t,J=6.0Hz),2.54(2H,t,J=5.8Hz),2.72(2H,m),3.37(2H,q,J=6.4Hz),3.40(1H,m),4.59(2H,t,J=7.0Hz),5.43(1H,s),5.45(2H,bs),7.23-7.34(10H,m),7.51(1H,t,J=7.6Hz),7.83(1H,d,J=8.4Hz),7.91(1H,s),7.94(1H,d,J=8.4Hz),8.59(1H,br)
【0099】(実施例26)
1-[3-(4-クロロルブタノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-ア

ミンの合成

1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミン0.24g(1mmol)をN,N-ジメチルホルムアミド30mlに懸濁し、4-クロロ酪酸0.11ml(1.1mmol)及び1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・塩酸塩0.29g(1.5mmol)を加え室温で1晩撹拌した。反応液に食塩水を加え、酢酸エチルで3回抽出した。有機層を食塩水で洗浄し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をエーテルさらに水でトリチュレートして沪取し、1-[3-(4-クロロルブタノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン30mg(0.0867mmol)を淡褐色粉末として得た。このものの分光学的データは以下の通りである。

【0100】IR(KBr)$cm^{-1}$:3330,3200,1650,1530

$^1$H-NMR(DMSO-$d_6$)$\delta$(ppm):1.91-2.04(4H,m),2.26(2H,t,J=7.4Hz),3.12(2H,q,J=6.2Hz),3.64(2H,t,J=6.6Hz),4.59(2H,t,J=6.8Hz),6.58(2H,br),7.26(1H,t,J=7.4Hz),7.45(1H,t,J=7.8Hz),7.62(1H,d,J=8.0Hz),8.03(1H,d,J=7.6Hz),8.05(1H,br),8.20(1H,s)

【0101】(実施例27)

1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンブタノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

1-[3-(4-クロロルブタノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン25mg(0.0722mmol)、4-(ジフェニルメトキシ)ピペリジン・塩酸塩44mg(0.144mmol)及び炭酸カリウム40mg(0.289mmol)をN,N-ジメチルホルムアミド3ml中で、100℃に加熱して8時間撹拌した。反応液に水を加え、クロロホルムで2回抽出し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をアルミナカラムクロマトグラフィーに付し、クロロホルム-メタノール(150:1~70:1v/v)溶出画分により目的物を集め、溶媒留去後エーテルでトリチュレートして、1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンブタノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン15mg(0.0260mmol)を白色粉末(mp:158~162.5℃)として得た。このものの分光学的データは以下の通りである。

【0102】IR(KBr)$cm^{-1}$:3200,1640,1530,1070,700

$^1$H-NMR($CDCl_3$)$\delta$(ppm):1.62(2H,m),1.77(4H,m),2.10(2H,m),2.19(2H,m),2.29(2H,t,J=7.0Hz),2.34(2H,t,J=6.4Hz),2.69(2H,m),3.35(2H,q,J=6.5Hz),3.40(1H,m),4.58(2H,t,J=7.0Hz),5.45(2H,bs),5.47(1H,s),7.19-7.34(11H,m),7.51(1H,t,J=7.7Hz),7.82(1H,t,J=8.4Hz),7.92(1H,s),7.93(1H,d,J=8.2Hz)

【0103】(実施例28)

1-[3-(5-クロロルペンタノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミン0.32g(1.33mmol)をN,N-ジメチルホルムアミド40mlに懸濁し、5-クロロ吉草酸0.15ml(1.46mmol)及び1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・塩酸塩0.38g(1.99mmol)を加え室温で1晩撹拌した。反応液に水を加え、酢酸エチルで2回さらにクロロホルム-メタノール(10:1v/v)で2回抽出した。有機層を食塩水で洗浄し、乾燥($Na_2SO_4$)後、溶媒を減圧下留去した。残渣をエーテルでトリチュレートして沪取し、1-[3-(5-クロロルペンタノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン0.16g(0.445mmol)を淡褐色粉末として得た。このものの分光学的データは以下の通りである。

【0104】IR(KBr)$cm^{-1}$:3470,3290,1650,1525,1395

$^1$H-NMR(DMSO-$d_6$)$\delta$(ppm):1.62(2H,m),1.70(2H,m),2.00(2H,t,J=7.0Hz),2.12(2H,t,J=7.4Hz),3.12(2H,q,J=6.3Hz),3.62(2H,t,J=6.2Hz),4.59(2H,t,J=6.9Hz),6.61(2H,bs),7.26(1H,t,J=7.6Hz),7.45(1H,t,J=7.8Hz),7.63(1H,d,J=8.4Hz),7.98(1H,br),8.04(1H,d,J=8.2Hz),8.21(1H,s)

【0105】(実施例29)

1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンペンタノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

1-[3-(5-クロロルペンタノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン50mg(0.139mmol)、4-(ジフェニルメトキシ)ピペリジン・塩酸塩42mg(0.139mmol)及び炭酸カリウム58mg(0.417mmol)をN,N-ジメチルホルムアミド3ml中で、100℃に加熱して7時間撹拌した。不溶物を沪過して除き、溶媒を減圧下留去した。残渣をアルミナカラムクロマトグラフィーに付し、

クロロホルム-メタノール（100：1～70：1v/v）溶出画分により目的物を集め、溶媒留去後エーテルでトリチュレートして沪取し、1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンペンタノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン20mg(0.0338mmol)を白色粉末(mp：152～154℃)として得た。このものの分光学的データは以下の通りである。

【0106】IR(KBr)cm$^{-1}$：3330, 3200, 2940, 1640, 1530, 1070, 700

$^1$H-NMR(CDCl$_3$)δ(ppm)：1.50(2H,m), 1.64(2H,m),1.69(2H,m), 1.84(2H,m), 2.08(2H,m), 2.19(2H,m), 2.20(2H,t,J=7.4Hz), 2.30(2H,t,J=7.2Hz), 2.70(2H,m), 3.36(2H,q,J=6.5Hz), 3.41(1H,m), 4.57(2H,t,J=7.0Hz), 5.45(2H,bs), 5.49(1H,s), 5.94(1H,t,J=5.8Hz), 7.21-7.37(11H,m), 7.52(1H,t,J=7.7Hz), 7.83(1H,d,J=8.4Hz), 7.90(1H,s), 7.92(1H,d,J=8.4Hz)

【0107】(実施例30)

1-[3-(6-ブロモヘキサノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

1-(3-アミノプロピル)-1H-イミダゾ[4,5-c]キノリン-4-アミン0.24g(1mmol)をN,N-ジメチルホルムアミド30mlに懸濁し、6-ブロモカプロン酸0.21g(1.1mmol)及び1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド・塩酸塩0.29g(1.5mmol)を加え、室温で1晩撹拌した。反応液に食塩水を加え酢酸エチルで2回抽出し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をエーテルさらに水でトリチュレートして沪取し、1-[3-(6-ブロモヘキサノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン50mg(0.120mmol)を灰白色粉末として得た。このものの分光学的データは以下の通りである。

【0108】IR(KBr)cm$^{-1}$：3330, 3200, 1540, 1540, 1395

$^1$H-NMR(DMSO-d$_6$)δ(ppm)：1.36(2H,m), 1.52(2H,m), 1.70(2H,m), 2.00(2H,m), 2.10(2H,t,J=7.0Hz), 3.11(2H,m), 3.60(2H,t,J=6.*8Hz), 4.59(2H,t,J=7.0Hz), 6.56(2H,bs), 7.25(1H,t,J=7.4Hz), 7.44(1H,t,J=7.4Hz), 7.62(1H,d,J=7.8Hz), 7.95(1H,br), 8.03(1H,d,J=7.4Hz), 8.20(1H,s)

【0109】(実施例31)

1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンヘキサノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミンの合成

1-[3-(6-ブロモヘキサノイルアミノ)プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン45mg(0.108mmol)、4-(ジフェニルメトキシ)ピペリジン・塩酸塩65mg(0.215mmol)及び炭酸カリウム59mg(0.430mmol)をN,N-ジメチルホルムアミド3ml中、100℃に加熱して8時間撹拌した。反応液に水を加えクロロホルムで2回抽出し、乾燥($Na_2SO_4$)後、減圧下溶媒を留去した。残渣をアルミナカラムクロマトグラフィーに付し、クロロホルム-メタノール（150：1～70：1v/v）溶出画分により目的物を集め、溶媒留去後エーテルでトリチュレートして沪取し、1-[3-[[4-(ジフェニルメトキシ)-1-ピペリジンヘキサノイル]アミノ]プロピル]-1H-イミダゾ[4,5-c]キノリン-4-アミン28mg(0.0462mmol)を微黄色粉末(mp：151～155℃)として得た。このものの分光学的データは以下の通りである。

【0110】IR(KBr)cm$^{-1}$：3330, 2940, 1630, 1540, 1070, 700

$^1$H-NMR(CDCl$_3$)δ(ppm)：1.31(2H,m), 1.48(2H,m), 1.63(2H,m), 1.70(2H,m), 1.86(2H,m), 2.07(2H,m), 2.17(2H,t,J=7.6Hz), 2.20(2H,m), 2.27(2H,t,J=7.6Hz), 2.71(2H,m), 3.37(2H,q,J=6.5Hz), 3.42(1H,m), 4.57(2H,t,J=6.8Hz), 5.45(2H,bs), 5.50(1H,s), 5.62(1H,t,J=6.0Hz), 7.21-7.37(11H,m), 7.53(1H,t,J=7.7Hz), 7.83(1H,d,J=8.4Hz), 7.90(1H,s), 7.93(1H,d,J=8.2Hz)

【0111】(実施例32)

製剤：本発明の化合物を含有する軟膏を以下の方法により調製した。

| | |
|---|---|
| 本発明化合物 | 0.2g |
| ソルビタンモノラウレート(SP-20) | 2.0g |
| ミリスチン酸イソプロピル(IPM) | 0.4g |
| 白色ワセリン | 7.4g |
| 全量 | 10.0g |

【0112】80℃に加熱したソルビタンモノラウレー※50※ト(SP-20)2gに本発明化合物0.2gを加え撹

拌溶解した。これにミリスチン酸イソプロピル（ＩＰＭ）０.４ｇを加えた後、別に加熱溶解（８０℃）しておいた白色ワセリン7.４ｇを加え、撹拌しながら室温冷却した。

【０１１３】（比較例１）

２%イミキモド軟膏の作成

８０℃に加熱したイソステアリン酸５ｇに米国特許４９８８８１５に記載の方法で合成したイミキモド０.５ｇを加え撹拌溶解した。これに、加熱溶解（８０℃）しておいた白色ワセリン１９.５ｇを加え、撹拌しながら室温冷却した。

【０１１４】（比較例２）

吉草酸ベタメタゾンの外用剤

０.１２%リンデロンＶ軟膏（シオノギ製薬）をそのまま使用した。

【０１１５】（実施例３３）

抗ヒスタミン作用

（１）試験方法

体重３００－６００ｇの雄性、Ｈａｒｔｌｅｙ系モルモット（購入先：ハムリー）を使用した。試験方法はT. Ｉｓｈｉｉらら（Naunyn-Schmiedeberg's Arch. Pharmaco l.,332,219-223,1986）により報告された方法を一部変更したものを用いた。モルモットを放血致死させた後、甲状軟骨から気管支分岐部までの気管を摘出し栄養液で満たされたシャーレに移す。気管周囲の組織をていねいに取り除いた後、輪状軟骨にそって幅２～３mmの横切切片を切り出し、その中の２片から気管筋標本を作成した。標本は３７℃に加温した栄養液（Krebs bicarbonate液：NaCl　１１８.１mM, CaCl₂　２.５mM, KH₂PO₄　１.２mM, KCl４.６mM, MgSO₄　１.０mM, NaHCO₃　２５mM, glucose　１１.１mM, pH：７.６５）を満たした１０mlマグヌス容器中に懸垂し、９５%O₂，５%CO₂の混合ガスを通気した。標本の初期負荷を１ｇとし、その等尺性張力変化を張力トランスデューサー（NEC San-ei,Type 45196A）及び歪圧力アンプ（NEC San-ei,Type 1236）を介してインク書レクチコーダー（RIKADENKI R-50）上に記録した。

【０１１６】標本は１時間 incubation してからヒスタミン（１０⁻⁵M）を投与して収縮反応を得た。これを数回繰り返し、標本の反応が安定になったのち実験に供した。被験化合物を２０分間前処置し、被験化合物投与前後のヒスタミンの収縮高から抑制率を求めた。

【０１１７】ヒスタミン二塩酸塩は生理食塩水に、イミキモド（１－イソブチル－１Ｈ－イミダゾ［４.５－ｃ］キノリン－４－アミン）、塩酸ジフェンヒドラミン及び本発明化合物はＤＭＳＯ（ジメチルスルホキシド）に溶解（ＤＭＳＯのマグヌス容器中での最終濃度は０.１%）した。

【０１１８】（２）結果

モルモット気管筋のヒスタミン収縮を５０%抑制する被験化合物の濃度（ＩＣ₅₀値）を以下の表１に示す。実施例２２、２４、２７、２９及び３１の化合物はジフェンヒドラミンと同様にヒスタミン収縮を強く抑制した。

【０１１９】

【表１】

表１

| 被験化合物 | 抗ヒスタミン作用（$IC_{50}$） |
|---|---|
| イミキモド | ＞$10^{-5}$M |
| 塩酸ジフェンヒドラミン | $1.5\times10^{-7}$M |
| 実施例２２ | $3.4\times10^{-7}$M |
| 実施例２４ | $4.0\times10^{-7}$M |
| 実施例２７ | $1.9\times10^{-7}$M |
| 実施例２９ | $3.4\times10^{-7}$M |
| 実施例３１ | $2.2\times10^{-7}$M |

【０１２０】（実施例３４）

皮膚好酸球浸潤抑制作用

（１）試験方法

動物は４週齢のＢａｌｂ／ｃマウス（雄）を日本クレア（株）より購入し１週間の順化期間の後に実験に供した。

【０１２１】①ダニ抗原液の調製

０.９%塩化ナトリウム水溶液２０mlにヤケヒョウヒダニ（Dermatophagoidespteronyssinus：International Biologicals,Inc.;Lot.No.14679）１ｇを添加し、３０mlのホモジナイズポットに移し、氷冷下、４０００～４５００rpmでホモジナイズした（顕微鏡下でホモジナイズ溶液を観察し、ダニの原形をとどめない程度までホモジナイズした）。ホモジナイズした溶液を５０mlの遠沈管に移し、室温で３５００rpmで５分間遠を行い、上澄を別の遠沈管に移した（溶液Ａ）。この操作を２回繰り返すことによって、溶液Ｂ、溶液Ｃを得た。精製水（ＲＯ水）で十分洗浄した透析膜（三光純薬(株)：Seamless Celluiose Tubinng）に、溶液Ａ，Ｂ，Ｃをそれぞれ封入し、４℃で０.９%塩化ナトリウム水溶液に対して一晩、透析を行った。透析終了後、溶液Ａ，Ｂ，Ｃのタンパク質量をタンパク定量キット（Protein assay Reagent BCA Kit：PIERCE,Inc.）で測定し、各々の溶液を５００μg/mlのタンパク濃度になるように、０.９%塩化ナトリウム水溶液で調製した。これらの３溶液を混合して１５mlのポリプロピレンチューブに１０mlずつ分注し、ダニ抗原溶液とした。この溶液は使用時まで－８０℃で凍結保存した。

【０１２２】②感作及び惹起

百日せき菌液をダニ抗原溶液に40分の１容量添加したものを感作溶液とした。感作はマイジェクター（テルモ社製）を用い、マウスの頸部の皮下にこの溶液を200μl投与することによって行った。この感作方法で初回感作を含め７日おきに三回感作を行った。

【０１２３】惹起は初回感作２１日後に、０.９%塩化

ナトリウム水溶液で２００μg/mlのタンパク濃度に調製したダニ抗原溶液を背部皮内にマイジェクター（テルモ社製）を用いて５０μl投与することによって行った。

【０１２４】㉔皮膚回収及び病理標本の観察

惹起４８時間後に頸椎脱臼によりマウスを屠殺し背部の皮膚を剥ぎ取り、マーキングした部分を中心に1cm四方に皮膚を切断した。回収した皮膚は１０％中性ホルマリン緩衝液（コーニングの１５ml遠沈管使用）に入れ１日以上室温に放置して固定した。固定した皮膚は、常法にしたがってパラフィン切片作成後、ルナ染色を施した（切り出しは体軸に対し垂直方向に皮膚サンプルの中央と頭側2mm上方の２カ所で行った）。標本の観察は光学顕微鏡（４００倍）で、１切片1cm当たりの好酸球数を計測した。薬剤（被験化合物）による抑制率は以下の式から算出した。

【０１２５】抑制率（％）＝｛（基材投与群の好酸球数－被験化合物投与群の好酸球数）／基材投与群の好酸球数）｝×１００

【０１２６】㉕各被験薬物の調製

実施例３２の方法により作製した。

【０１２７】㉖薬物投与方法

経皮投与（密封包帯法：Occlusive dressing technique＊（ＯＤＴ））

マウスをエーテル麻酔して背部中央を電気バリカンで皮膚を傷つけないように除毛した。背部中央の惹起箇所にあたる部分にあらかじめ油性マジックで印を付けた。薬剤（被験化合物）の塗布は、背部の印をつけた部分を中心に前投与では3cm四方に、惹起後は惹起部分を中心に2cm四方に塗布した。さらに、塗布部を覆うようにラップをのせ伸縮性テープ（Johnson & Johnson MEDICAL INC：エラスコチン）で固定した。対照群は基材のみを塗布した。投与量は一匹当たり５０mgとし、投与スケジュールは以下のように惹起前日より３日間連投した。

【０１２８】惹起前日→惹起日（惹起直後）→惹起翌日（計３回）

【０１２９】（２）結果

２％イミキモド軟膏、実施例化合物の２％軟膏、０．１２％吉草酸ベタメタゾン軟膏の各被験薬物のダニ惹起マウス皮膚好酸球浸潤反応に対する抑制効果を表２、３に示す。実施例の化合物の多くは好酸球浸潤を吉草酸ベタメタゾン軟膏と同等以上に抑制した。

【０１３０】

【表２】

表２

| 投与薬物 | 匹数 | 好酸球数（個/cm） | 抑制率（％） |
|---|---|---|---|
| 非感作動物 | | | |
| 非惹起 | 3 | 0.33±0.33 | － |
| 感作動物 | | | |
| ダニ惹起 | | | |
| 基材軟膏 | 5 | 519.8±129.96 | － |
| ２％イミキモド軟膏 | 5 | 154.0± 33.22 | 70.37 |
| 実施例２２の化合物（２％軟膏） | 5 | 237.6± 53.76 | 54.29 |
| ０．１２％吉草酸ベタメタゾン軟膏 | 5 | 261.6± 50.64 | 49.67 |

【０１３１】

※　※【表３】

表３

| 投与薬物 | 匹数 | 好酸球数（個/cm） | 抑制率（％） |
|---|---|---|---|
| 非感作動物 | | | |
| 非惹起　(std) | 2 | 12.00±3.00 | － |
| 感作動物 | | | |
| ダニ惹起 | | | |
| 基材軟膏　(cont) | 7 | 371.42± 71.03 | － |
| 実施例２２の化合物（２％軟膏） | 5 | 217.40± 88.51 | 41.46 |
| 実施例２４の化合物（２％軟膏） | 5 | 61.80± 11.84 | 83.36 |
| 実施例２７の化合物（２％軟膏） | 5 | 235.60± 97.18 | 36.56 |
| 実施例２９の化合物（２％軟膏） | 5 | 362.00± 97.75 | 2.53 |
| 実施例３１の化合物（２％軟膏） | 4 | 159.75±131.83 | 56.99 |

惹起２日後の好酸球数を各群 mean±S.E. で示した。

【０１３２】（実施例３５）

<u>２相性耳浮腫抑制作用</u>

（１）試験方法

★動物は４週齢のＢａｌｂ／ｃマウス（雄）を日本クレア（株）より購入し１週間の順化期間の後に実験に供した。

33

【0133】③感作及び惹起
感作及び惹起は澤田らの方法に準じて行った（アレルギー，43（8），p1099,1994）。すなわち、卵白アルブミン（OVA）1μgと水酸化アルミニウムゲル（alum）4mgを含む生理食塩液250μlを腹腔内投与して感作した。さらに、2週間後に同様の方法で追加感作を行った。惹起は2回目の感作10日後にエーテル麻酔下に5μgOVA（20μl）を耳に皮内注射した。惹起においては、注射の影響を除くためOVAの代わりに生理食塩液のみを投与する群を設けた。

【0134】④2相性耳浮腫反応の測定
OVAで惹起すると1時間と24時間後にピークとなる耳浮腫反応が生じるので、このときの耳の厚みをダイアルシックネスゲージを用いて測定し、これらの厚みに対する薬物と被験化合物の効果を検討した。

【0135】⑤薬物投与方法
薬物及び被験化合物は1%カルボキシメチルセルロース（CMC）に懸濁し、惹起24時間前と2時間前に経口あるいは腹腔内に投与した。溶媒コントロール群には1%CMCのみを投与した。そして以下の式より薬剤（被験化合物）により抑制率を算出した。

【0136】抑制率（%）＝｛（OVA惹起薬物投与群の耳の厚み－生食惹起溶媒投与群の耳の厚み）／OVA惹起溶媒投与群の耳の厚み－生食惹起溶媒投与群の耳の厚み）｝×100

34

【0137】（2）結果
表4に示す通り、実施例22の化合物は32mg/kgの経口あるいは腹腔内投与で即時型及び遅発型の耳浮腫反応を同用量のイミキモドよりも強く抑制した。

【0138】
【表4】

表4

| 投与薬物 | 投与量 | 例数 | 抑制率（%） | |
|---|---|---|---|---|
| | | | 即時型 | 遅発型 |
| イミキモド | 32mg/kg ig | 4 | 0 | 16.4 |
| 実施例22 | 32mg/kg ig | 4 | 91.8 | 100.0 |
| | 32mg/kg po | 5 | 28.6 | 41.4 |
| デキサメタゾン | 1mg/kg po | 4 | 23.8 | 64.4 |

【0139】
【発明の効果】上述した通り、本発明により新規なアミド誘導体が得られる。本発明のアミド誘導体は、抗ヒスタミン効果及び好酸球浸潤抑制効果により、即時型及び遅発型のアレルギー反応を強く抑え、特にアトピー性皮膚炎の治療に有用である。

---

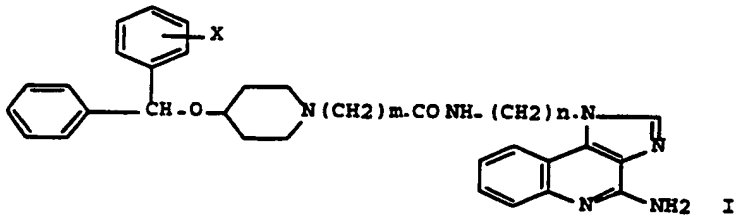
フロントページの続き

(72)発明者　飯塚　貴夫
神奈川県足柄上郡中井町井ノ口1500番地
テルモ株式会社内

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2000 ACS
AN 1997:542873 CAPLUS
DN 127:248129
TI Preparation of imidazo[4,5-c]quinoline-containing amides and their intermediates and pharmaceuticals for atopic dermatitis
IN Nanba, Ryoichi; Ishii, Takeo; Nishida, Hitoshi; Iizuka, Takao
PA Terumo Corp., Japan
SO Jpn. Kokai Tokkyo Koho, 18 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI JP 09208584 | A2 | 19970812 | JP 1996-13113 | 19960129 <-- |

OS MARPAT 127:248129
GI



I

AB Title compds. I (X = H, halo; m = 1-9; n = 2-12), which show eosinophil infiltration inhibition and antihistaminic activity, are prepd. Eight types of intermediates for I are also claimed. An EtOH soln. contg. 0.12 g 1-[3-(acrylamino)propyl]-1H-imidazo[4,5-c]quinoline-4-amine (prepn. given), 0.13 g 4-(diphenylmethoxy)piperidine.HCl, and NaHCO3 was refluxed overnight to give 75 mg I (X = H, m = 2, n = 3), which in vitro inhibited histamine-induced contraction of tracheal muscle of guinea pig with IC50 of 3.4 .times. 10-7 M, vs. 1.5 .times. 10-7 M, for diphenhydramine.HCl. An ointment contg. I was formulated.